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Design of the Flexible HORSE Morcellator for the Surgical Treatment of Cushing's disease in Horses

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BITE

Challenge the future

CONTENTS

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***Abstract* - Cushing's disease is a neurological disorder caused by the loss of dopamine secretion in and near the pituitary gland. This loss causes the formation of hormone secreting tumors in the pituitary gland, subsequently leading to the occurring symptoms of the disease. Since first discovery of Cushing's disease in horses in 1932, no great breakthroughs have been made in the treatment of this disease in horses. Unlike in human Cushing's disease, where surgical removal of the pituitary tumors is a common treatment modality, in horses oral treatment is the treatment of choice. This oral treatment does not provide a long-term solution to the disease, as it is focused on symptom reduction and does nothing to fight the actual cause of the disease.**

In collaboration with the department of Veterinary medicine Utrecht, a new paradigm of surgical treatment of Cushing's disease in horses has been developed that uses the vascular system in combination with an innovative flexible morcellator to reach the pituitary gland. This flexible HORSE morcellator incorporates a rigid tip with a resection tool and a flexible shaft which incorporates a cable drive element, used for actuating the resection tool, and a central tissue transportation lumen. Full tissue resection from the surrounding structures is achieved by a radial rotating resection tool with serrated cutting teeth in combination with a cutting edge at the rigid tip of the morcellator; thereby integrating both the action and reaction forces within the instrument. The radial rotating cutting blade is actuated with an axial translating cable mechanism, achieving low bending stiffness and high axial stiffness in a minimal cross-sectional diameter of 0.3 mm leaving sufficient room for the tissue transportation lumen. Finally, the incorporation of aspiration in the flexible shaft is used for contact initiation and tissue transportation from the distal to the proximal end.

The flexible HORSE morcellator was tested at the University Utrecht on a horse cadaver for the validation of the resection tool design, drive element design and feasibility of the endovascular approach. In the tests the morcellator was successfully inserted using the facial vein and subsequently successfully guided towards the pituitary gland, validating the endovascular approach. While inserted, the morcellator was able to resect the pituitary gland tissue from the surrounding tissue. Furthermore, the cable drive mechanism and aspiration system of the HORSE morcellator were validated since smooth actuation of the resection tool was observed whilst maintaining flexibility of the shaft, and both contact initiation and tissue transportation was achieved.

***Keywords-* Morcellation, Cushing's disease, horses, endovascular, catheter, design.**

I. INTRODUCTION

A. Cushing's Disease: Horse versus Human

Since the first discovery of Cushing's disease in humans in 1912, the disease has been discovered in multiple other species including dogs, donkeys and horses. Cushing's disease in horses, (also known as Pituitary Pars Intermedia Dysfunction (PPID)), was first reported in the German veterinary literature in 1932 and is one of the most common neoplastic diseases in elderly horses [8, 9]. Multiple studies have determined a prevalence of 33-40% in adult horses [8].

By definition, Cushing's disease is a naturally occurring, clinical progressive pituitary gland disorder. The pituitary gland is a relatively small endocrine gland located near the skull base of the brain. It can be found in all mammals and generally consists of three distinct lobes, i.e. the pars distalis, pars intermedia and pars tuberalis, each responsible for the production and subsequent secretion of a variety of closely related peptides. Most of the body's endocrine systems are controlled by the pituitary gland, including temperature, growth, blood pressure, energy metabolism and urine production [10, 11]. Additionally, the pituitary gland controls almost all other glands that are responsible for hormone secretion, like the adrenal and thyroid gland.

Cushing's disease is caused by the loss of dopamine innervation (and secretion) in and near the pituitary gland [12]. The loss of dopamine secretion increases the hormone production of the pituitary gland and is causative for the formation of multiple endocrine-active adenomas, i.e. hormone secreting tumors. As a result, the production of the hormone cortisol by the cortex of the adrenal gland will increase. This inhibitory hormone is (in healthy subjects) part of a negative feedback loop that influences the hormone production, in particular AdrenoCorticoTropic Hormone (ACTH), of the pars distalis lobe and thus lowers the overall hormone production by the pituitary gland. The pars intermedia lobe; the main position of the adenoma in Cushing's disease in horses, however, is part of a feedforward system that cannot be controlled by cortisol, but is under dopaminergic control, making it more difficult to treat than with human patients where the main position is the pars distalis lobe.

The cortisol excess (in combination with the heightened levels of hormones produced by the pituitary gland) leads to the clinical symptoms of Cushing's disease. Clinical signs include (among others) the appearance of dorsal fat pads around the stomach area, skin disorders, abnormal hair growth patterns, also known as hirsutism, glucose intolerance (diabetes mellitus) and weakness of the muscles [13]. In many patients, the clinical manifestations of the disease are progressive, such that over time the affected patients may develop additional symptoms. Furthermore, untreated Cushing's disease may lead to severe illness and even death. Unfortunately, no cure has yet been found for the disease and current treatment is aimed at lessening the severity of the clinical signs.

In this paper a new paradigm in the surgical treatment of Cushing's disease in horses will be discussed. An innovative instrument will be designed for the surgical treatment of Cushing's disease in horses with future application in humans in mind.

B. Treating Cushing's Disease

A recent study has determined that Cushing's disease in horses has multiple similarities to human Cushing's disease, including disease pathology and progression [8]. Even so, a very different approach is taken in the treatment of horses. Instead of surgical removal of the adenomas, as regularly performed in humans [13], in horses oral medication is the most common treatment modality. Treatment is aimed at controlling and reducing the severity of the clinical signs of the disease, rather than removing the adenoma from the pituitary gland, due to the fact that to date this is technically impossible and as so has never been performed.

Conversely, the surgical removal of the adenomas using one of three surgical approaches, which are the transnasal, transseptal and transcranial approach, as illustrated in Fig. 1, is a common treatment modality in humans [11]. In the first two approaches, the nasal cavity and sphenoid sinus; a hollow space just beneath the pituitary gland (see Fig. 1), are used to obtain access to the pituitary gland. The main difference between these two approaches can be found in the used entry point to the nasal cavity; in the transseptal approach an incision is made under the upper lip, whereas in the transnasal approach one or both nostrils is used. In both techniques access to the pituitary gland is gained by drilling through the sphenoid sinus. The third surgical approach for the treatment of Cushing's disease in humans is the transcranial approach, or craniotomy. In this procedure, a rectangular piece of bone is removed from the skull to access the front side of the brain. The brain is then lifted and moved a bit backwards to gain access to the pituitary gland.

Unfortunately, all the above mentioned surgical approaches are not applicable for pituitary surgery in horses. Even though the position of the pituitary gland is comparable in horses and humans, the shape and dimension of the skull is very different (see Fig. 2). In the transnasal approach the instrument will need to travel a considerably longer distance, in the range of 50 to 60 cm (in comparison to human pituitary surgery where a distance of only 7 to 8 cm has to be bridged), due to the elongated nostrils and more backward position of the pituitary gland in the skull. Furthermore, the more backward position of the pituitary gland and the thickness of the skull around the gland, requiring to drill through more than a centimeter of bone in total to reach the sphenoid sinus and pituitary gland, makes using this entry point not feasible. The second approach; the transseptal approach, can potentially be performed in two different ways, i.e. via an incision in the upper lip and nasal cavity (as with the transnasal approach) or via the palate. Using the palate to reach the pituitary gland, as is often performed in dogs, is difficult since the horse cannot open the mouth with a sufficient angle to allow for a straight path to the pituitary gland. This will result in heavily restricted maneuverability of the surgical instrument and the need for a curved tool. Additionally, the same constraint as the transnasal approach, i.e. thick skull around the pituitary gland, makes using both the transseptal approaches not feasible in horses. Finally, the third approach; the transcranial approach is, according to an expert veterinarian, also not considered feasible due to the thick bony mass that needs to be traversed (> 1-2 cm) and the shape of the skull around the brain, which does not allow easy access to the ventral side of the brain. Additionally, this approach is not preferable since brain damage may occur due to lifting and moving the brain.

As the surgical approaches currently applied for human pituitary surgery are not applicable, a new paradigm in pituitary surgery in horses was developed in close collaboration with an expert veterinarian of the Faculty of Veterinary Medicine in Utrecht. In contrast to the human vascular system, in the horse multiple superficial veins, like the facial vein, can provide direct access to the pituitary gland. With a diameter of maximum 10 mm, this superficial vein can be used to dispose a flexible instrument towards the pituitary gland. A procedure that has been previously performed by Irvin et al. (1987) and the expert veterinarian to measure the hormone production by the pituitary, has shown the feasibility of this method to reach the pituitary gland. As such this procedure will be utilized and altered for the purpose of the current design challenge [14]. The procedure is illustrated in Fig. 3. The instrument will be inserted in 'S' by using the facial vein (1) and is subsequently guided towards the deep facial vein (2), advanced through the vena reflexa into the ophthalmic vein (4), and finally guided into the intercavernous sinus (9) (the extension of the cavernous sinus (8)); the outflow duct of the pituitary gland. Whereas, in the previous procedure of Irvine et al. the catheter was fixated at this position for data collection, the new approach will continue on with the surgical removal of the pituitary adenomas. Note that, removal of the adenoma or entire pituitary gland could potentially result in the need for administration of supplement hormones to the horse. However, according to expert veterinarians, these hormones are less expensive than the dopaminergic compound used nowadays and will not result in a relapse of the disease.

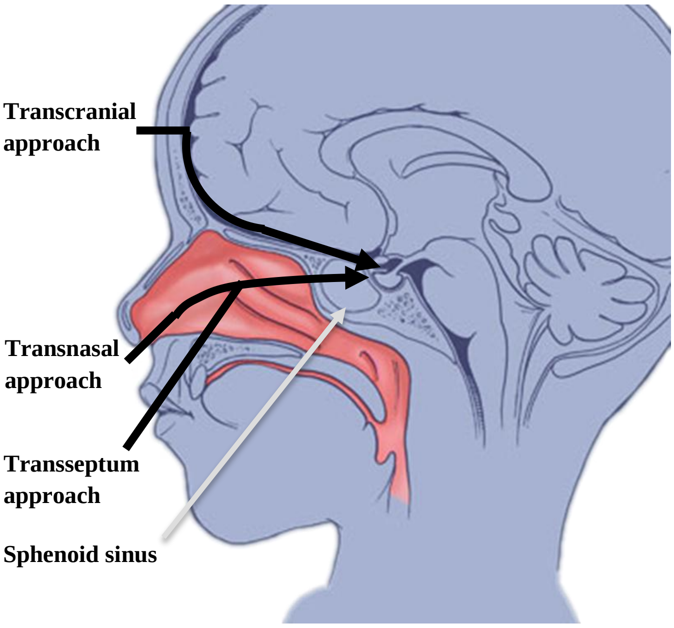


Fig. 1: Three surgical approaches in human pituitary surgery [11].

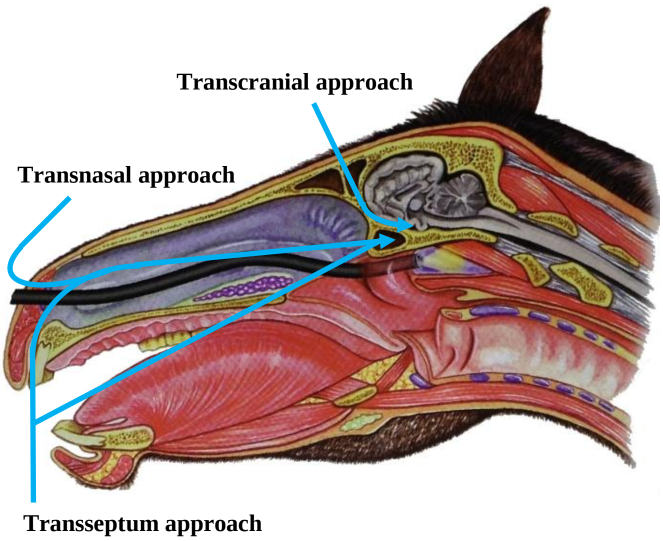


Fig. 2: Three surgical approaches to the pituitary gland in humans applied on the horse [15].

A. *Problem Definition*

New ways to surgically treat Cushing's disease in horses is a necessity to provide a more effective treatment for the horse owners [9, 12]. Especially so, since the incidence of equine Cushing's has increased over the last two decades [16]. Surgical treatment in affected horses has multiple advantages over the oral medication used to date, the most prominent being the acute treatment of the cause of the occurring symptoms (instead of symptom control), resulting in long-term improvement of the clinical signs and no relapse of the disease.

The treatment modality of choice; oral medication, does not provide an effective treatment modality for the disease and is rather expensive, with costs rising up to 400 euros per month, which most horse owners are unable to afford, according to multiple expert veterinarians. The prognosis of Cushing's disease in horses is highly dependent on the effect of the pharmaceutical medicine (which differs per horse), the observed clinical signs, the progression of the disease, and the willingness of the owner to properly manage the horse [9, 12]. Well-managed horses are anticipated to live approximately 5 to 7 years. However, in severely affected horses the life-span can shorten dramatically [12].

Even though surgical treatment in humans has improved in the last decade, the life-expectancy of humans suffering from pituitary disorders is still variable and dependent on the surgical outcome and patient-related factors. At present, not all tumors can be reached due to size restriction of the entry point (size of the nostrils), position and size of the tumor, and lack of maneuverability of the current instruments due to rigid design. Therefore, in the near future, designing a flexible instrument for pituitary surgery in horses that incorporates improved maneuverability can potentially aid in improving human pituitary surgery as well.

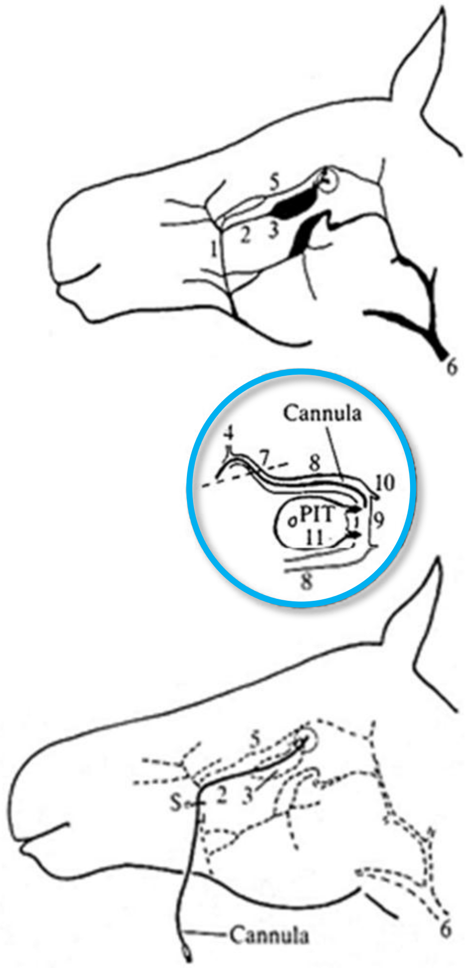


Fig. 3: Catheter insertion procedure. The Cannula is inserted into the facial vein (1) at the position S. (2): deep facial vein, (3): sinus of the deep facial vein, (4): ophthalmic vein, (5): transverse facial vein, (6): jugular vein, (7): entry of the deep facial vein into the cranial cavity, (8): cavernous sinus, (9): intercavernous sinus, (10): connections to the ventral petrosal sinus, (11): pituitary gland: the site of entry of the two pituitary veins is indicated with arrows (at (9)). Picture adapted from [14].

To find potential removal methods for the surgical removal of the pituitary gland using the vascular system, a literature survey was performed (see Appendix A). The literature survey determined mechanical morcellation; a surgical technique that is used for the division and subsequent removal of soft tissue mass in the abdomen during laparoscopic surgery, as a potentially feasible removal method for surgical treatment of Cushing's disease in horses [17]. In this thesis current mechanical morcellators, that use a moving cutting blade for division of the tissue and a grasper or aspiration as means of tissue transportation, are used as a starting point to design a new flexible mechanical morcellator for the surgical treatment of Cushing's disease in horses.

B. *Goal of this Study*

The goal of this study is to design, prototype and test a flexible horse morcellator which can reach the equine pituitary gland using the vascular system and subsequently remove the adenoma or entire pituitary gland to provide a more effective therapy for Cushing's disease in horses as to potentially realize a longer life-span for the affected horses.

C. *Layout of this Study*

In this study the whole process of the development of the morcellator for the surgical treatment of equine Cushing's disease will be discussed. First, in Chapter 2 the state of the art mechanical morcellators will be explained and subdivided into categories based on their working principle. Graphical illustrations of current morcellator design will be provided and the need for redesign explained. Based on the findings in this Chapter, first design decisions will be made. In Chapter 3 the design process of the surgical tool will commence. The design requirements of the entire morcellator, resection tool, driving element and other notable elements will be drafted. Finally, at the end of Chapter 3 a decision is made for the final design of the morcellator. In Chapter 4 the prototype development and assembly will be discussed. The prototype will be graphically illustrated using schematic and actual illustrations of the final design. The working mechanism of the endovascular approach, drive element, and resection tool, will be tested. The test set-up is schematically illustrated, followed by the results of the morcellator tests. The results, improvement points, and possible spin-off into human and other medical applications, will be discussed in Chapter 5 and in Chapter 6 a conclusion will be made.

II. MORCELLATORS – STATE OF THE ART

A. *Morcellators and their Applications*

A major hurdle to the development of laparoscopic surgery has been the availability of effective extraction techniques for the removal of larger tissue masses through small incisions [18]. In 1973 the first hand driven morcellator was developed to facilitate large tissue mass removal during laparoscopic surgery [19, 20]. The term 'morcellator' refers to the verb 'morcellation' and entails the division of compliant tissue into pieces, followed by their removal [21]. The tissue to be divided into pieces can be any type of compliant tissue mass, for example located in the abdominal area or colon, such as the uterus, gallbladder or prostate. Besides the division of compliant tissue into pieces, the morcellator facilitates transport of the tissue out of the body through a small incision or natural orifice like the vagina. Nowadays, morcellators are relatively frequently used in clinical practice. Common laparoscopic procedures performed using a morcellator as main minimal invasive instrument are hysterectomies, myomectomies, splenectomies, and prostatectomies [21]. However, each specific surgical field has its own range of specialized morcellation instruments and methods.

There are various different types of morcellators on the market today. This paper will focus on mechanical morcellators, i.e. morcellators that exclusively use one or multiple cutting edges for soft tissue resection. All types of morcellation instruments engage and transport the tissue using one of two approaches; these are the manual approach using a small minimal invasive grasper, or the aspiration approach. In the manual approach the traction force (used for contact initiation) is created by grasping the tissue with the minimal invasive grasper and subsequently moving it towards the distal cutting edge of the morcellator as is illustrated in the left illustration in Fig. 4. Continuation of the retraction motion of the minimal invasive grasper towards the proximal end of the morcellator will transport the tissue away from the operation area. In the aspiration approach the pressure difference between the distal and proximal end of the morcellator is used to create the needed traction force to bring the tissue into contact with the cutting edge and subsequent transportation as illustrated in the right illustration in Fig. 4. For safety reasons, the tissue is always pulled towards the distal cutting edge of the morcellator rather than moving the morcellator towards the tissue.

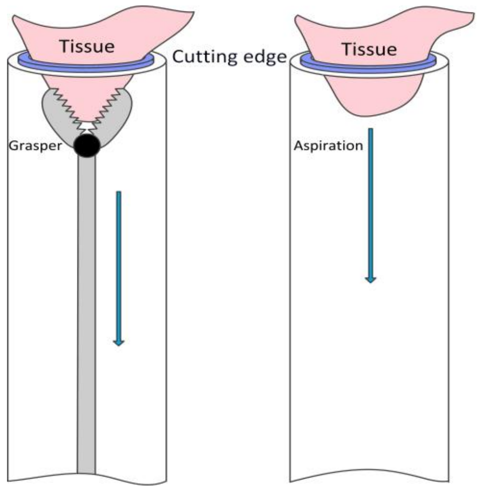


Fig. 4: Morcellation contact initiation and transportation methods. Left: manual approach using a minimal invasive grasper for contact initiation with the cutting edge (purple) and tissue (pink) transportation. Right: aspiration approach using pressure difference for contact initiation with the cutting edge (purple) and tissue (pink) transportation. The blue arrows indicate the direction of the force on the tissue and tissue transportation direction.

Four main types of mechanical morcellators are discussed in literature, i.e. coring, peeling, nibbling and shaving morcellators, as illustrated in Fig. 5. In the ***Coring*** method the tissue mass is pulled towards a rapidly rotating (750-1000 rpm) hollow cylindrical blade (similar to a rotating tubular razor blade) of the device by means of a grasper. As a result, the cylindrical blade cores out tissue from the larger tissue mass, categorizing this cutting technique as coring. ***Peeling*** is a debulking process very similar to coring; it deviates in working principle in that it uses an oblique sleeve that partially shields the circular cutting blade from the tissue. This oblique shield prevents the morcellator from coring into the tissue mass, and enables the device to stay in contact with the peeled-off mass, facilitating a continuous tissue removal process. In the ***Nibbling*** method the tissue is morcellated by an inner translationally reciprocating cutting blade which is continuously sliding back and forth across an opening in the outer tube, thereby 'nibbling' small pieces of tissue from the main tissue mass. Finally, ***Shaving*** entails the use of a rapidly rotating drill bit, which can have any shape ranging from straight and serrated blades to regular drills, that shaves off any tissue that comes into contact with it.

By focusing on the resection tool used by the different type of morcellators, two fundamental differences can be found. The most prominent being the position of the resection tool; which is either located at the distal tip of the morcellator, categorizing this as ***frontal resection***, or is located along the contour of the morcellator, categorizing this as ***sideways resection***. The second fundamental difference can be found in the way the tissue is divided from the environment. The morcellator either uses one cutting edge for delivering the action force on the tissue; the reaction force of the resection action being provided by other means than the resection tool, categorizing this method as ***single-sided resection***, or two or more cutting edges for delivering of both the action and reaction force on the tissue, categorizing this as ***double-sided resection***. In Table 1 the different morcellation methods are subdivided into these categories. The columns represent the main resection principles used by the different morcellation methods, i.e. single-sided and double-sided resection; the rows represent the position of the resection tool, i.e. frontal or sideways resection.

As can be seen, in Table 1 two question marks arise. These question marks represent the gaps in current morcellator design. Currently there are no morcellators available that utilize either frontal double-sided resection or sideways single-sided resection. As such, these gaps provide potential design opportunities for the flexible morcellator design. However, design opportunities can also be found in current morcellator designs as will be discussed in the next section.

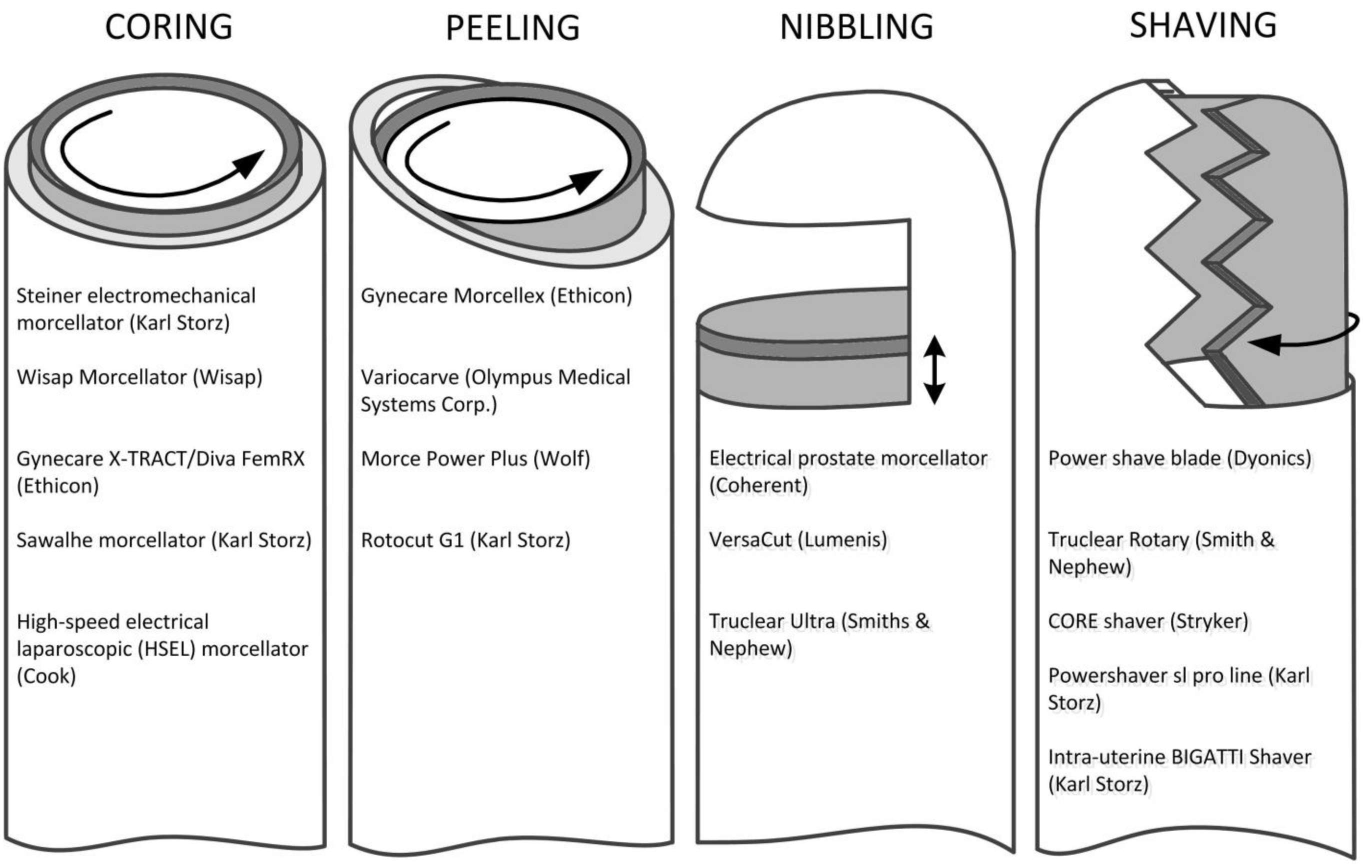


Fig. 5: Schematic illustrations of mechanical morcellator types, i.e. coring, peeling, nibbling and shaving, found in literature with corresponding clinical morcellators currently in use. The resection tool is indicated in grey and the cutting edge of the morcellator in dark grey. The black arrows indicate the direction of motion of the resection tool [21]. For extra information and illustrations of the different morcellator refer to Appendix B.

B. *Clinical Need for Redesign*

From design perspective, using the vascular system as surgical entry point to the pituitary gland will put considerable constraints on the surgical instrument. The instrument should be able to maneuver inside the vascular system, requiring the use of a flexible shafted instrument. The dimensions of the vascular system, like the diameter, length and bending radius, will determine the final outside dimensions and required bending stiffness of the instrument. Furthermore, the instrument should be able to accommodate the removal of the total pituitary volume of approximately $8.0 \cdot 10^3$ mm^3.

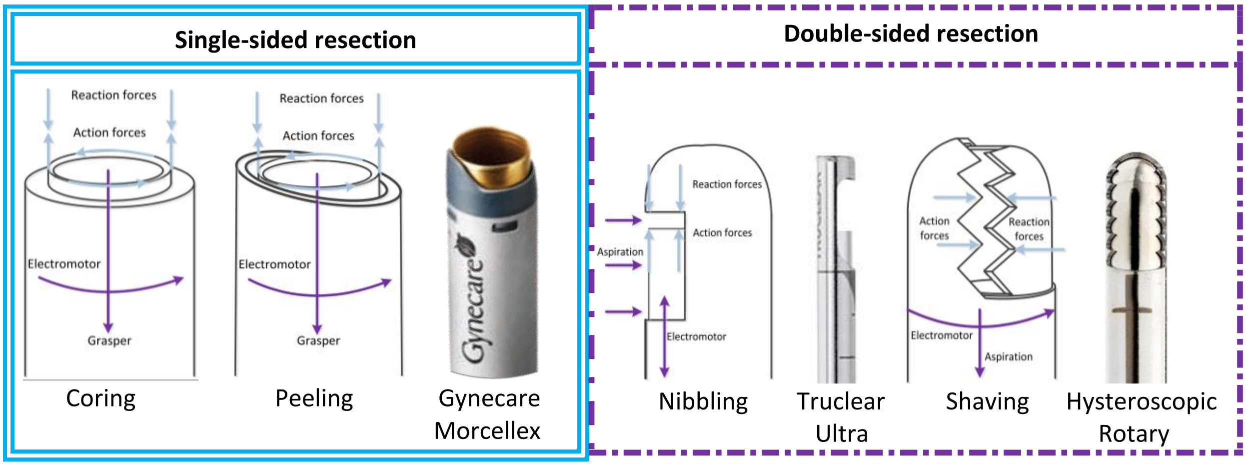
The difference in application of current mechanical morcellators used in clinical practice makes a complete redevelopment of morcellator design, of either an existing design or a design gap, a necessity for endovascular pituitary removal. In this section the main redesign points of the current morcellator designs will be discussed as well as some design criteria in respect to the endovascular approach. Some design decisions will already be made based on this analysis.

In standard minimally invasive surgery, the use of an incision and inflation techniques allows for rigid instrument designs that pivot around the incision point. However, when using the vascular system, the use of a rigid instrument is not possible; instead a flexible instrument with a rigid tip length that is capable of (passive or active) steering through the vascular system is necessary to perform the needed surgical procedure. Unfortunately, all morcellators found in literature are not flexible. However, morcellators that require a rigid tip length (defined as the maximum rigid length the resection tool requires for resection in the direction of the main instrument axis) that is equal to the effective resection length (defined as the maximum cut-off length that can be achieved in one resection cycle) are preferred over morcellators that require a larger rigid tip length than the effective resection length. These morcellators can accommodate potentially smaller bending radii. The required rigid tip length in comparison to the effective resection length is, if one looks at the current morcellator designs, in the shaving, coring and peeling morcellators equal to the resection length. In the morcellators utilizing the nibbling principle, however, the required rigid tip length is larger than the effective resection length, due to the reciprocating inner blade.

Furthermore, in the nibbling and shaving method the tissue size that can be removed in one cycle is dependent on the dimensions of the rigid tip length. Resection of bigger tissue size per cycle will require a larger rigid tip length, whereas in the peeling and coring method, the tissue size is independent of the rigid tip length. Since minimal rigid tip length in combination with fast tissue removal is preferred for the endovascular approach, an optimum must be found between the rigid tip length, morcellation speed and tissue size per cycle.

Table 1: Fundamental differences of current morcellator designs. The rows represent the resection direction, i.e. frontal or sideways resection. The columns represent the resection principle, i.e. single-sided or double-sided resection [22-24].

		Resection principle	
		Single-sided resection	Double-sided resection
Resection position	Frontal resection	1	?
	Sideways resection	?	2



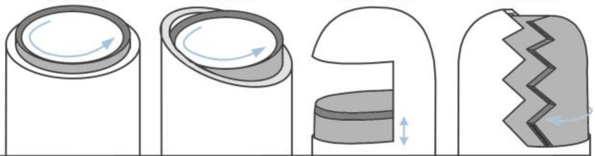
Consecutive and simultaneous instrument insertions are relatively common and easily performed during laparoscopic surgery. However, by using the vascular system as entry point, multiple simultaneous or consecutive instrument insertions are not feasible due to the small cross-sectional diameter and longer distance the instrument needs to travel. The increased risk of blood loss and damage to the veins and surrounding structures also makes this not desirable. Therefore, one single morcellation instrument needs to be able to fully dissect and transport the tissue away from the surrounding structures. From the mechanical morcellators used in clinical practice, only the shaving and nibbling morcellators comply with this requirement. The coring and peeling morcellators do not comply with this requirement, since they require the use of another tool (scalpel or grasper) for full tissue resection, since they only core out a cylindrical tissue strip, comparable to that of an apple drill. Furthermore, the use of a minimally invasive grasper for contact initiation that is used in the coring and peeling method is not feasible due to the flexible nature of the shaft of the morcellator. Therefore, the choice is made to use aspiration for contact initiation and tissue transportation.

In combination with the need for a resection tool that allows for full tissue resection from the environment, it is imperative to have the action and reaction force integrated in this tool to prevent high forces on the surrounding tissue. High forces on the surrounding tissue, like the (in close proximity of the pituitary situated) circle of Willis, the brain and other important structures as the hypothalamus will increase the chance of unwanted tissue damage. Furthermore, omitting the reaction force does not allow for high precision resection as it cannot be predicted beforehand where stress concentration will appear. The morcellators utilizing the nibbling and shaving method have both the action and reaction force integrated within the instrument. However, it must be noted that the morcellators utilizing the shaving method can either cut or tear the tissue depending on the type of shaver blade used. By tearing the tissue, the inertia of the surrounding tissue is used for resection and the reaction force is only partly delivered by the shaver; subsequently negatively affecting the chance of tissue damage and resection precision. The coring and peeling method only provide the action force for resection; the reaction force is delivered by the tissue, surrounding structures, and minimal invasive grasper. The precision of resection using the coring and peeling method can therefore not be accurately predicted and are thus not considered feasible resection methods for the endovascular pituitary removal method.

Finally, to minimize the chance of relapse, as is often the case with the current oral medication, it is important to remove the adenomas as a whole, leaving only healthy pituitary tissue behind. An important factor influencing the chance of total adenoma removal is the reachability inside the sella turcica; the saddle-shaped depression in the sphenoid bone on which the pituitary gland rest. Since, the pituitary gland lies in an ellipsoid shaped room, most optimal reachability can be obtained by a forward functioning resection tool located at the distal tip of the instrument, as is the case for the frontal resection tools of the coring and peeling morcellators. Resection tool locations other than at the distal tip, as with sideways resection, will decrease the reachability, in particular at the back of the sella turcica. This is the case in the shaving and nibbling morcellator.

In Table 2 an overview of the different morcellator types and their compliance to the above mentioned requirements is given. As can be seen, the morcellators in clinical practice do not comply with the complete set of requirements for catheter based pituitary removal. Redesign or complete redevelopment is necessary to utilize a morcellator in the flexible endovascular approach for the surgical treatment of Cushing's disease in horses. In the next Chapter, the design process of the flexible morcellator will commence, resulting in a design that is applicable for endovascular treatment.

Table 2: Review of current mechanical morcellators types, i.e. coring, peeling, nibbling and shaving, based on the requirements discussed in this section that are important for the redesign for the endovascular pituitary approach.



	CORING	PEELING	NIBBLING	SHAVING
RIGID TIP LENGTH	Equal	Equal	Larger	Equal
POSITION DISSECTION TOOL	Frontal	Frontal	Sideways	Sideways
ACTION AND REACTION FORCE	NO	NO	YES	YES
SINGLE INSTRUMENT RESECTION	NO	NO	YES	YES

III. DESIGN

A. *Introduction*

There is no universal language for design. This has led to many differing philosophies and approaches to a design process. As a result, no two design processes are equal. However, one aspect is always similar; a design process is iterative in nature. This iterative nature is often not emphasized in literature due to the difficulties in the creation of a clear structure. Unlike the linear design process that is described in literature, with the entire set of design requirements illustrated at the beginning of the process, in the current presented research the design requirements are drafted and expanded during the design process. Multiple iterations will lead to the entire set of requirements to which the instrument should comply.

To emphasize the iterative nature of the design process, the design requirements to which the morcellator should comply are discussed in levels. At the various phases of the morcellator design process the respective important requirements are detailed and discussed. This will give a more clear picture and understanding of the origin of the different design requirements and design process.

The design process will start constructing an innovative flexible morcellator using a basic morcellator structure, which will consist of the following parts:

- Rigid tip
  - Resection tool
  - Transmission element
- Flexible shaft
  - Drive element (with actuator)
  - Tissue transportation lumen

The requirements are subdivided into three main categories:

- Dimensions of the morcellator
- Resection element requirements
- Drive element requirements

Within the stated design requirements, multiple brainstorm sessions were held to find potential design solutions for the resection and drive element. The solutions were reviewed to find fundamental differences between the solutions. By subdivision of the solutions in the categories representing these fundament differences, gaps in the brainstorm were identified and subsequently filled. A comparison of the different solutions led to the development of the most feasible designs and finally, at the end of this Chapter, the choice is made for the final design of the morcellator.

B. Tip Dimensions

The dimensions of the rigid tip element (in which the resection tool and possible transmission are located) and flexible shaft of the morcellator are set by the clinical environment in which the morcellator operates. Unfortunately, no information is available on the dimensions, i.e. diameter, length, bending radius, of the vascular system of the equine head, necessitating the need for three experiments to determine these dimensions. In the Faculty of Veterinary Medicine in Utrecht these experiments were performed on horse cadavers. The cadavers where drained of blood and the facial veins of the three cadavers were exposed. The drained diameter of the facial vein of the three cadavers was measured and determined at 6 mm in diameter, see Fig. 6. However, since the diameter of the veins will decrease closer to the pituitary gland; a maximum diameter of 5 mm of the instrument is set. This requirement is based on an expert opinion of a veterinarian specialized in catheter interventions in the horse.

The minimal required length of the morcellator is determined by inserting a radiopaque catheter (type: DELVO CH07 FR X RAY PORGES NEOPLEX, 3 mm diameter) in a median section of an (adult dutch warmblood)

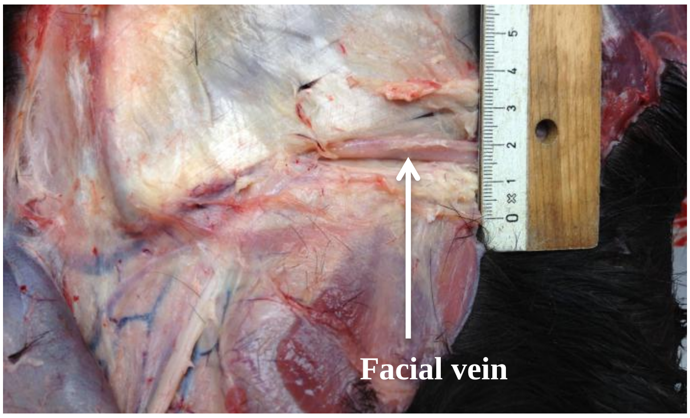


Fig. 6: The facial vein exposed on an adult Dutch warm blood horse. The diameter of the vessel is determined to be 6 mm in diameter (without blood flow).

equine head in the Faculty of Veterinarian Medicine under the guidance of an experienced veterinarian. In Fig. 7 and 8 the procedure is graphically illustrated. The catheter was inserted using the facial vein and subsequently guided through the vascular system until the catheter reached the pituitary gland, which was verified by eye by dissecting and lifting the skull and brain from the equine head. The catheter was subsequently marked at the insertion site and removed from the vascular system where it was measured. The minimal required length was determined at: 30 cm. However, to compensate for anatomical differences, 5 cm of length is added to the catheter, bringing the required total length of the morcellator to 35 cm.

Consecutive to the measurement of the minimal length of the catheter, the minimal bending radius was determined by taking an X-ray in the sagittal plane of the horse head with the catheter placed therein. In Fig. 9 this is illustrated. The minimum bending radius with the catheter was determined at 21 mm. The diameter of the catheter was used (3 mm) to scale the image. No X-ray was taken in the coronal and traverse plane, since according to the expert veterinarian the bending radius exclusively lies in the sagittal plane. The maximum length of the rigid tip (L) is a direct result of the minimum bending radius, as illustrated in Fig. 10, and follows from Equation (1) and (2):

$$x = (R - r_{blood\ vessel}) + \emptyset_{instrument} \quad (1)$$

$$L = \sqrt{(R + r_{blood\ vessel})^2 - x^2} \quad (2)$$

With:

x =	Instrument tip equation [mm].
L =	Maximum rigid tip length [mm].
R =	Minimum bending radius of vein, measured from the centerline of the vein [mm].
$r_{blood\ vessel}$ =	Radius of the blood vessel [mm], with a maximum of 6 mm.
$\emptyset_{instrument}$ =	Diameter of the instrument [mm], with a maximum of 5 mm.

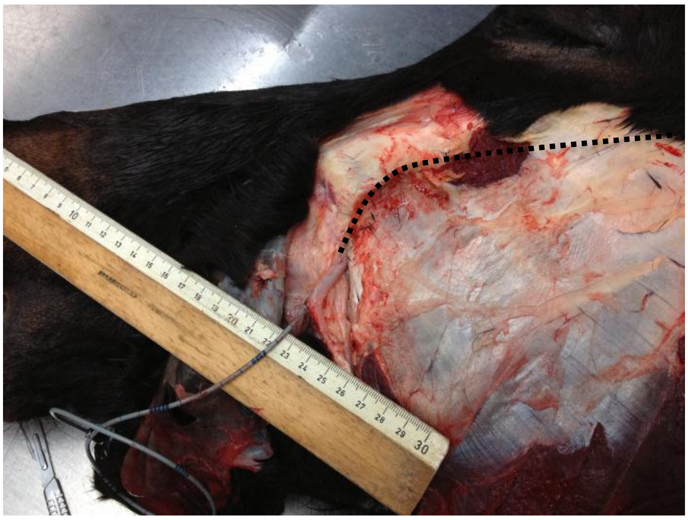


Fig. 7: The radiopaque catheter, with a diameter of 3 mm, inserted in the facial vein. The dotted line indicates the path that the catheter travels towards the pituitary gland.

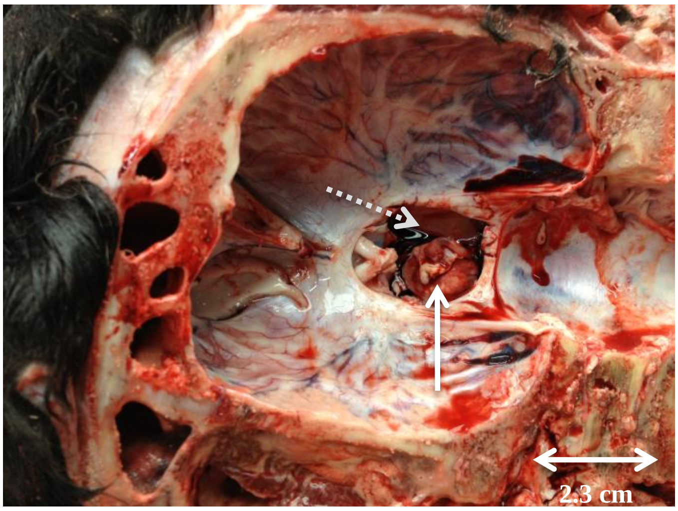


Fig. 8: Skull base of a horse. The entry point of the catheter is indicated with the dotted arrow. The pituitary gland is indicated with an arrow. Note: the nose of the horse is to the left of this picture.

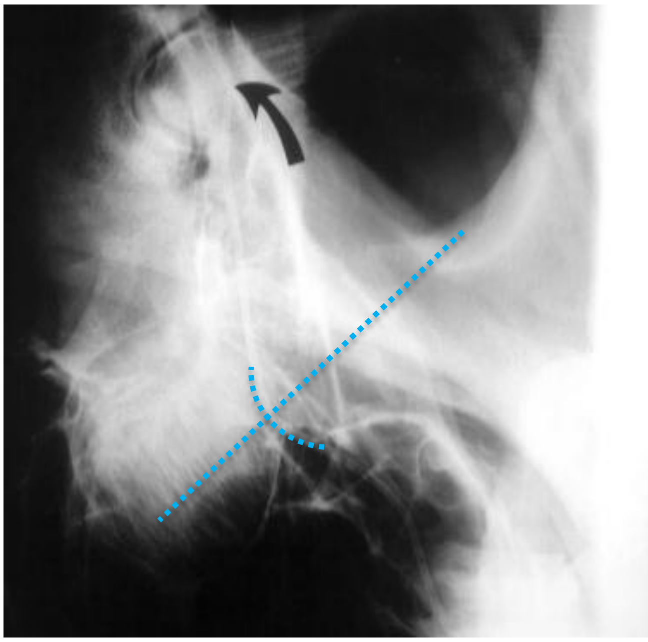


Fig. 9: X-ray image of the radiopaque catheter (diameter 3mm) inserted in the facial vein. The black arrow indicates the position of the catheter. The blue dotted lines indicate the bending radius of the catheter in this plane.

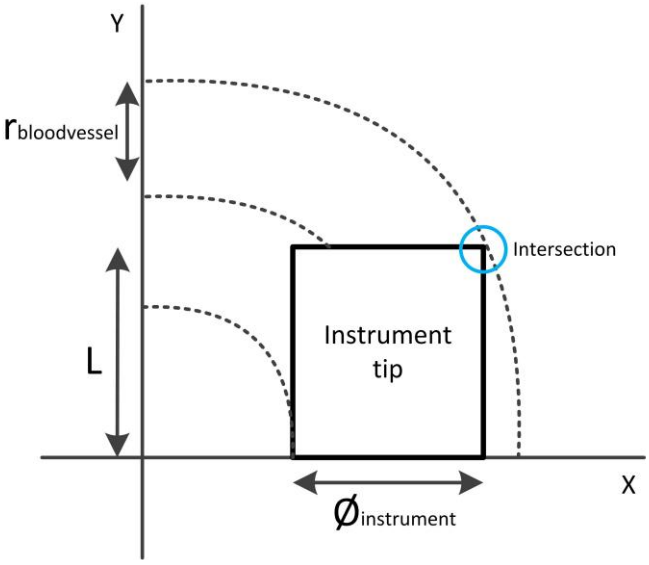


Fig. 10: Schematic overview of a blood vessel (indicated with the dotted line) with an inserted catheter with a rigid tip.

By filling in Equating (1) with R = 21 mm, $r_{\text{blood vessel}}$ = 6 mm, $Ø_{\text{instrument}}$ = 5 mm, a maximum rigid tip length of 18.1 mm is obtained. However, it must be noted that the blood vessels do show some flexibility; allowing for slightly longer tip lengths.

C. Resection Element

1) Resection Element Design Requirements

The resection element will facilitate the resection or division of the tumorous pituitary tissue from the surrounding (healthy) tissue. For this purpose the resection element (and transmission element if necessary) will be integrated inside the rigid tip of the morcellator, which will be positioned in close proximity of the pituitary gland. The dimensional constraints set by the vascular system of the equine head, only allowing for a maximum outer diameter of 5 mm and a maximum length of 18 mm of the morcellator tip, determine the maximum dimensions and shape of the resection tool (and potential transmission element). Furthermore, the dimensions of the sella turcica, the ellipsoid shaped room wherein the pituitary gland is located, has led to the decision to position the resection tool at the frontal distal tip of the morcellator.

The endovascular nature of the procedure necessitates that the resection tool facilitates full tissue resection from the environment without the use of another instrument, since this potentially increases the chance of unwanted tissue damage and surgery time. After successful catheter insertion and placement of the morcellator in close proximity of the pituitary gland, the resection tool should provide the retention of aspiration before and during resection to obtain contact initiation between the resection tool and tissue and subsequent tissue transportation. Furthermore, during resection, the action and reaction forces need to be part of a direct force loop integrated within the resection tool to prevent (high) reaction forces on the environment, potentially leading to unwanted tissue damage.

Finally, directly following resection, the resection tool design will allow for tissue transportation by avoiding (complete) blockage of the central transportation lumen of the morcellator. Clogging of the morcellator will be prevented by taking the dissected tissue size into account when designing the size of the transportation channel.

2) Resection Element Design Directions

Current morcellator designs, as illustrated in Table 1 do not comply with the resection element design requirements. Only one category (from Table 1) remains that complies with the main design directions, i.e. the double-sided frontal resection category. This category is defined as such that the morcellators in this category divide the tissue from the environment by using a resection tool located at the frontal distal tip that delivers both the action and reaction force on the tissue by means of reducing the surface area of an opening between a series of at least two cutting blades. No morcellators were found that utilize this method for morcellation; thus providing a design opportunity for the new flexible morcellator design.

To get a comprehensive overview of the direction of the forces that can be utilized for double-sided frontal resection, the double-sided frontal resection category is further subdivided into axial, radial, tangential, or a combination of these directions, as is illustrated in Fig. 11. In the axial approach the tissue is dissected with the action and reaction force in the direction of the main instrument axis of the morcellator. In the tangential approach the action and reaction forces for resection follow the contour of the morcellator and in the radial approach the tissue is dissected using action and reaction forces perpendicular to the main instrument axis. From this figure it becomes clear that the design choice for a frontal resection tool in combination with the design requirement to integrate both the action and reaction force inside the morcellator, will eliminate axial, tangential, axial + tangential and axial + radial resection, since this will lead to sideways resection. Only two feasible directions of the resection action remain, i.e. radial resection and radial + tangential resection.

The direction of motion of the resection tool must provide the needed resection action (and thus forces) at the tip of the morcellator, i.e. radial and radial + tangential resection. The cylindrical shape of the morcellator allows the morcellator to be subdivided into two major planes (instead of three) in which the direction of motion of the resection tool can be completely defined; an axial plane in the direction of the main instrument axis and a radial plane, perpendicular to the instrument axis. Both planes allow for translation and rotation in this plane; leading to four major motions that the resection tool can potentially utilize for resection, i.e. axial rotation, axial translation, radial translation, and radial rotation. However, the choice for a radial or radial + tangential resection action will eliminate axial translation as direction of motion of the resection tool, since this motion is perpendicular to the desired force direction and can therefore not achieve a force component in the radial or tangential direction. Therefore, three directions of motion for the resection tool remain:

- Axial rotation
- Radial translation
- Radial rotation

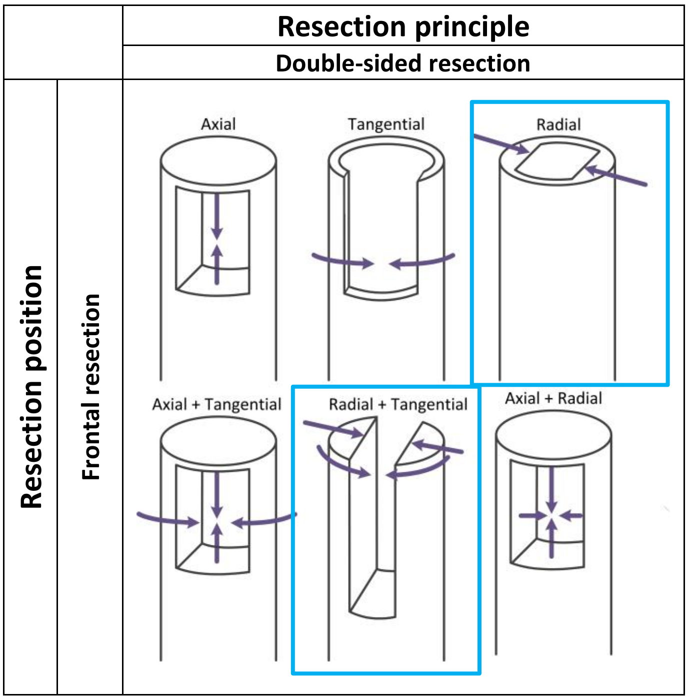


Fig. 11: Section 1:2 from Table 1; frontal double-sided resection. Within this category six potential directions of the resection forces can be utilized for resection; axial, tangential, radial, axial + tangential, radial + tangential and axial + radial resection. Only two feasible directions of resection forces, i.e. radial or radial + tangential resection, comply with the requirements as discussed in this section. These two directions are indicated with the two blue rectangular boxes.

D. Drive Element

1) Drive Element Design Requirements

The resection tool is actuated using one or more drive elements. The drive element will transfer the energy from the actuator towards the resection tool. The placement of the actuator determines the type of driving element that is needed for energy transfer. Local actuation will require the use of a short and stiff driving element, whereas remote actuation will require the use of a longer flexible driving element. The maximum diameter of the morcellator of 5 mm in combination with the need for a hollow inner tube for tissue transport towards the proximal end, has led to the decision for remote or proximal end placement of the actuator.

Current technology only allows for flexible transference of either axial translation or rotation from the proximal end of the morcellator towards the distal end; flexible transference of an in a radial plane translating or rotating driving element is not possible without the use of a transmission. Therefore, the decision is made that the driving element of the morcellator will either translate or rotate in the axial plane. The axial translating or axial rotating drive element should accommodate high axial stiffness or high torsion stiffness respectively in combination with low bending stiffness (350-500 Nmm^2). High axial stiffness in combination with low bending stiffness can be achieved by an axially incompressible or non-extendable mechanism. High torsion stiffness can be achieved by a mechanism that does not allow for twisting around the center line of the instrument. Low bending stiffness is difficult to achieve with the high torsion stiffness requirement needed for rotation, but can be relatively easily achieved with high axial stiffness. Therefore, axial translating driving elements are preferred over axial rotating driving elements.

Finally, the last step of the morcellation process; the removal and transportation of tissue debris from the operation area necessitates the incorporation of a transportation lumen in the morcellator. The drive element design should leave room for this transportation lumen.

2) *Drive Element Design Directions*

A short literature search determined different flexible drive elements that can potentially be incorporated into the final design. The designs are illustrated in Table 3. It must be noted that the overview is not comprehensive. A subdivision is made in unidirectional and bidirectional driving elements. In the unidirectional drive elements, the elements can only be used for rotation or translation in one direction and in the bidirectional driving elements, the elements can be used for rotation and translation in the two opposing directions. A further subdivision is made in the translating driving elements category, between push and pull. No drive elements were found that only support translating pull motion. Note that buckling of the driving element is prevented by a guidance structure inside the morcellator and as such is not taken into further consideration in the review of the drive elements.

The designs are reviewed based on the functional requirements of the drive element. Hollow shafted driving elements or drive elements that require a small cross-sectional area for functional operation (<0.5 mm) are preferred over larger solid driving elements, since this will allow for easy integration of a tissue transportation lumen. Size restrictions make the simplicity of the driving element design an important decision making factor. Minimal number of parts and low complexity of these parts are preferred. Furthermore, designs that are off the shelf available are preferred, since this prevents long manufacturing time. Finally, the torsion, axial, and bending stiffness of the parts is important. Designs dependent on the size of connection parts or dimensional constraints for high torsion or axial stiffness are not preferred, since by downscaling the stiffness will be negatively affected. Furthermore, designs where the axial/torsional stiffness is directly related to the bending stiffness are not preferred, since an increase in axial/torsional stiffness in these designs will lead to an increase in bending stiffness.

In Table 3 the review of the different drive element designs with the different review elements (noted above) are illustrated. Even though, some conclusions can already be drawn from this table, the close connection with the resection tool design necessitates the final choice for the driving element to be made in combination with the resection tool design.

E. *Drive versus Resection Element*

1) *Drive versus Resection Matrix*

Combining both the direction of motion of the drive element with that of the resection element, leads to the functional matrix illustrated in Table 4. The rows of the matrix represent the direction of motion of the drive element, i.e. axial translation or rotation. The columns represent the direction of motion of the resection element, i.e. radial translation or rotation and axial rotation. Several brainstorm session were held to fill the matrix with design possibilities (see also Appendix C). The most feasible options are illustrated in Table 4.

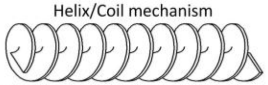
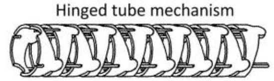
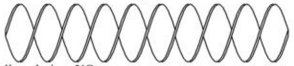
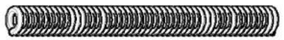
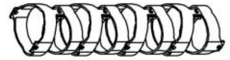
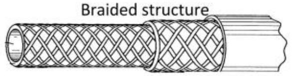
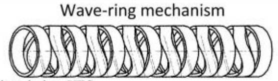
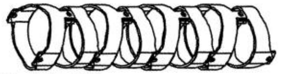
The different design possibilities are constructed out of the following elements: (1) a static outer element, (2) a resection tool, (3) a driving element and if needed (4) one or more transmission elements [1] .The diameter of the outer element is set to 5 mm, following from the dimensional constraints of the vascular system. A wall thickness of 0.3 mm is chosen for all the different elements and a minimal diameter of 0.5 mm for hinges. Clearance of 0.05 mm between the elements is chosen to ensure proper functioning and fit of the elements. All the designs incorporate two cutting edges that cut at the frontal distal tip of the instrument. One mechanism is responsible for opening as well as closing the resection tool to reduce morcellator complexity. Complete sealing of the hollow transportation channel with a closed resection tool will prevent clogging of the morcellator during insertion. Fast tissue removal is ensured by maximizing the diameter of the transportation channel and effective resection area. Finally, all the designs incorporate a closed outer element (except from distal tip where the resection tool is located) to prevent damage to the vascular system.

2) *Drive and Resection Design Directions*

In this section important factors are discussed that aid in the decision process for the determination of the final tip design. The difficulties and opportunities of the combination of the resection and drive element design are determined and some decisions are made.

[1] A transmission element is defined as a part or construction that changes the direction or type of motion, i.e. from translation to rotation or vice versa.

Table 3: Functional matrix of flexible drive elements found in literature. A subdivision is made between axial rotating and axial translating drive elements [1-7].

Axially rotating drive axis		Axially translating drive axis		
Unidirectional	Bidirectional	Unidirectional		Bidirectional
		Push	Pull	
Helix/Coil mechanism  Hollow design: **NO** No. elements: **1** Off the shelf available: **NO** Torsion stiffness dependent on: **Geometry / Dimensions** Bending stiffness dependent on: **Geometry / Dimensions**	Layered flexible drive shaft  Hollow design: **Available in hollow and solid design** No. elements: **Dependent on number of layers (>1)** Off the shelf available: **YES** Torsion stiffness dependent on: **Number of layers** Bending stiffness dependent on: **Number of layers**	Hinged tube mechanism  Hollow design: **YES** No. elements: **1 (laser cut joints)** Off the shelf available: **NO** Axial stiffness dependent on: **Structural strength joints** Bending stiffness dependent on: **Dimensions parts**	?	Compliant joint mechanism  Hollow design: **YES** No. elements: **1** Off the shelf available: **NO** Axial stiffness dependent on: **Geometry (strength joints)** Bending stiffness dependent on: **Geometry joints**
Twisted strip mechanism  Hollow design: **NO** No. elements: **1** Off the shelf available: **NO** Torsion stiffness dependent on: **Geometry / Dimensions** Bending stiffness dependent on: **Geometry / Dimensions**	Hinged tube mechanism  Hollow design: **YES** No. elements: **1 (laser cut joints)** Off the shelf available: **NO** Torsion stiffness dependent on: **Structural strength joints** Bending stiffness dependent on: **Dimensions parts**	Tightly wound spring  Hollow design: **YES** No. elements: **1** Off the shelf available: **YES** Axial stiffness dependent on: **Compression strength** Bending stiffness dependent on: **Geometry / Dimensions**		Spine mechanism  Hollow design: **YES** No. elements: **>> Dependent on length** Off the shelf available: **NO** Axial stiffness dependent on: **Structural strength joints** Bending stiffness dependent on: **Dimensions parts**
Coil spring  Hollow design: **YES** No. elements: **1** Off the shelf available: **YES** Torsion stiffness dependent on: **Geometry / Dimensions** Bending stiffness dependent on: **Geometry / Dimensions**	Braided structure  Hollow design: **YES** No. elements: **Dependent on number of layers (>1)** Off the shelf available: **YES** Torsional stiffness dependent on: **Number of layers** Bending stiffness dependent on: **Number of layers**	Wave-ring mechanism  Hollow design: **YES** No. elements: **>> Dependent on length** Off the shelf available: **NO** Axial stiffness dependent on: **Compression strength** Bending stiffness dependent on: **Dimensions rings**		Flexible cable  Hollow design: **NO** No. elements: **1** Off the shelf available: **YES** Axial stiffness dependent on: **Compression / Yield strength** Bending stiffness dependent on: **Dimension cable (Ø)**
Wounded leaf spring  Hollow design: **YES** No. elements: **1** Off the shelf available: **NO** Torsion stiffness dependent on: **Geometry / Dimensions** Bending stiffness dependent on: **Geometry / Dimensions**	Spine mechanism  Hollow design: **YES** No. elements: **>> Dependent on length** Off the shelf available: **NO** Torsion stiffness dependent on: **Structural strength joints** Bending stiffness dependent on: **Dimensions parts**			

The number of parts of the morcellator should be minimized. The minimization of the number of functional elements of the driving element and resection tool is an important aspect in minimizing friction losses, determining the manufacturability, ease of assembly, reliability, force delivery and precision of the morcellator. Increasing the number of parts will lead to higher instrument complexity and will as such potentially negatively affect the above mentioned points. In addition, the increase in complexity will significantly increase the chance of device failure. Friction losses will decrease the force delivery on the tissue and backlash between the parts can potentially decrease the overall precision at which the morcellator can be operated. Furthermore, Size restrictions set by the vascular system, in combination with the flexible nature of the morcellator, makes friction losses from the proximal to the distal end an important factor to take into account. The design of the drive element should minimize the friction with the outer element of the morcellator by minimizing the contact area between the two elements or by the incorporation of a smart bearing mechanism. By default, hollow drive element design with transportation lumen incorporation will necessitate use of friction decreasing measures, whereas solid drive elements with a cross-sectional area 10-100 times smaller than the outer diameter (5 mm) of the morcellator do not necessarily need to be designed for friction reduction.

Besides from the friction reduction, the force delivery at the cutting edge of the morcellator can be maximized by taking into account the direction of motion and design of the drive element, the resection tool design, and design of the transmission element.

The type of motion of the drive element, i.e. axial translation or axial rotation, will determine the way in which the force delivery can be increased and what the theoretical maximum force delivery is. The maximum force delivery in an axial translating driving element is highly dependent on the maximum axial force on the driving element, which in turn is dependent on the Yield strength of the element (neglecting friction). The maximal force that can be delivered in an axial rotating resection tool is highly dependent on the maximum torque on the driving element, which in turn is dependent on the maximum shear stress of the drive element, diameter and minimum bending radius of the morcellator (in this case: Ø5 mm and R=21 mm). The efficiency of the transference towards the resection tool, potentially using a transmission element, and the maximum stress, determine the final force delivery on the tissue. In this final step, stress limitations of the transmission elements, like hinges and cams, should be taken into account. These elements are, together with the drive element, the most vulnerable parts of the morcellator due to the size restrictions.

Fast tissue removal and the prevention of clogging the morcellator should be enabled by maximizing the size of the central transportation lumen. The transmission element should not interfere with the tissue transportation process and should preferably not obstruct the transportation lumen. The size of the tissue removed per cycle, which depends on the combination of the resection area and resection tool design, should be as large as possible. However, at the same time, the size of the tissue transportation lumen needs to be taken into account. The removed tissue size should be smaller than the transportation lumen diameter, preventing clogging of the morcellator during resection. Furthermore, the use of an unidirectional continuous cutting action is preferred over a bidirectional cutting action. A bidirectional cutting action requires a change in the direction of motion of both the resection tool and drive element. This change in direction will lead to high forces on the transmission elements and a decrease in the effective resection time.

F. Conceptual Morcellator Design

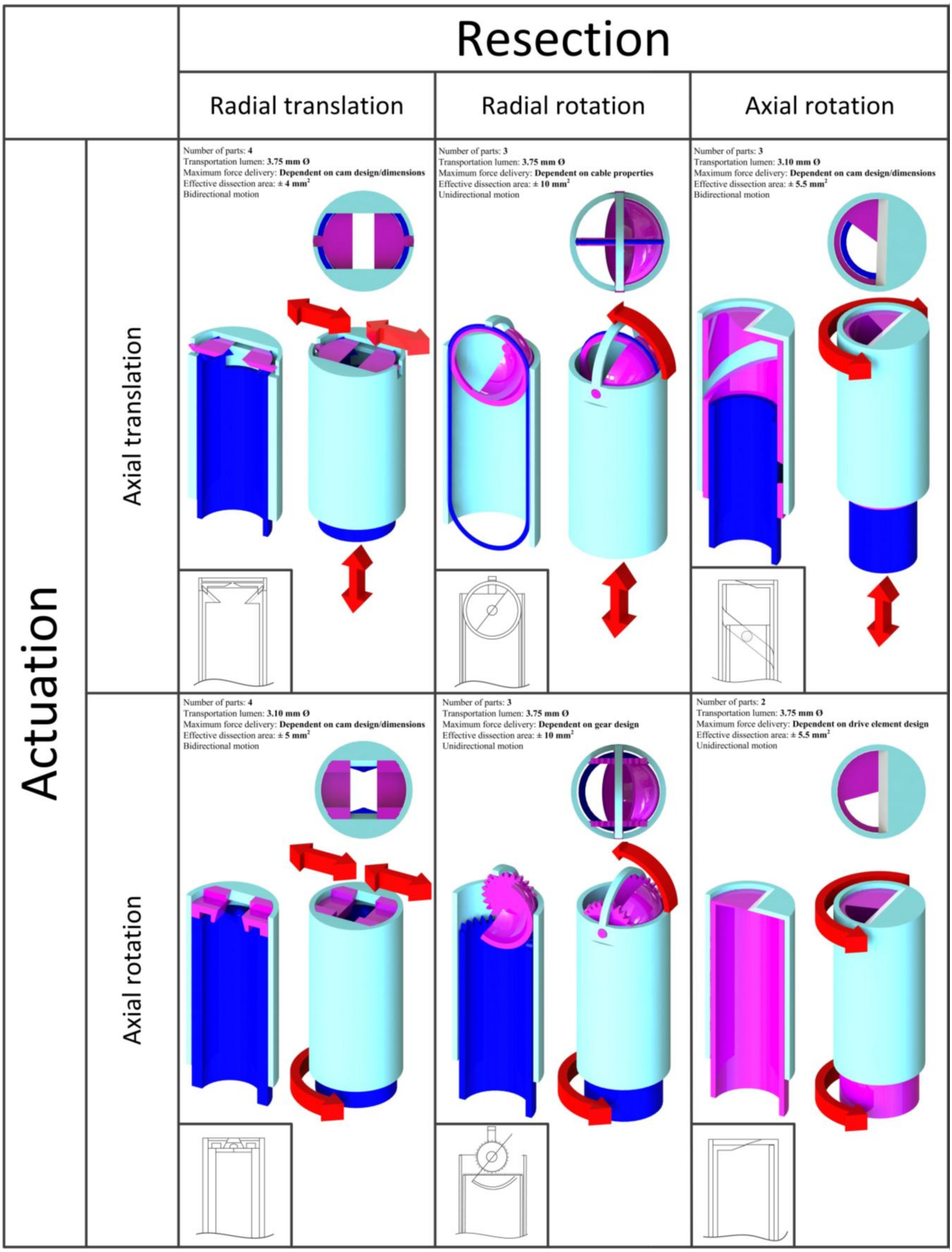
The combination of the resection tool with the associating drive element will form the rigid tip and flexible shaft of the morcellator. In Table 3 and 4 the review of the final design directions, as discussed in the previous section, for the different designs (both resection tool and drive element) are illustrated.

The final morcellator design should, most importantly, be able to dissect the tissue from the surrounding structures. To achieve this, the forces from the proximal end of the morcellator should be transferred towards the distal end (and thus resection tool) via a flexible drive element. The drive element should incorporate (low) bending stiffness in combination with high axial or torsional stiffness. Due to size restrictions and the flexible design, drive element designs that incorporate low bending stiffness in combination with high torsional are technically difficult to achieve. The choice is therefore made to utilize an axial translating drive element for the actuation of the resection tool of the morcellator.

As illustrated in Table 3, there are multiple drive element designs that can potentially be utilized for flexible actuation of the resection tool. The axial translating drive element designs are subdivided into designs that can either push, pull, or can facilitate both push and pull. No designs were found that can facilitate only pulling actions. A choice is made to use a flexible cable as axial translating drive element for the morcellator design. This drive element is off the shelf available in many different shapes, sizes and materials. Furthermore, this drive element has the lowest complexity of all the designs and does not rely on the structural strength of hinges or other fragile structures for achieving high axial stiffness, making it possible to transfer high forces from the proximal to the distal end of the morcellator with a minimal cross-sectional diameter of the cable. High friction losses inside the shaft of the morcellator are prevented, since the contact area between the drive element and flexible shaft of the morcellator is minimized due to the small cross-section.

Next to the force delivery requirement of the morcellator, the theoretical resection speed, i.e. the volume of the dissected tissue divided by the resection time, is an important deciding factor in determining the most feasible final design. The resection speed of the morcellator is dependent on multiple factors, including (among others) the effective resection area, shape of the resection tool, size of the transportation lumen

Table 4: Final six conceptual morcellator designs. Rows represent actuation direction of motion of the driving element. Columns represent the direction of motion of the resection element. Color-indications: Red: direction of motion, Pink: cutting blades, Blue: drive element, Light green: outer element.



and the use of an unidirectional or bidirectional resection tool. From all the designs illustrated in Table 4 that utilize an axial translating drive element, the design that potentially results in the highest resection speed is the design that utilizes a radial rotating resection tool, illustrated in column 2. This design incorporates the highest effective resection area and an unidirectional moving resection tool. Furthermore, this design incorporates a spherical resection tool design instead of a flat resection tool, resulting in the highest resection volume per cycle.

The final morcellator will thus incorporate an axial translating cable drive element with the radially rotating resection tool as is illustrated in Table 4 and Fig. 12. The axial translating motion of the cable drive element will be transferred to the radial rotating motion by means of friction, between the resection tool and the cable, and the use of two hinges connected to the resection tool. The friction between the cable and the resection tool should be sufficient to provide smooth energy transfer and prevent slip between the cable and resection tool. Furthermore, to achieve the continuous axial translating motion of the cable drive element, the cable ends of the drive element will be connected to achieve a continuous element. An axial rotating actuator will be used in combination with a pulley to provide the continuous transference of the axial rotating towards the axial translating motion (see Fig. 12).

In the next Chapter this design will be expanded towards a fully functional prototype.

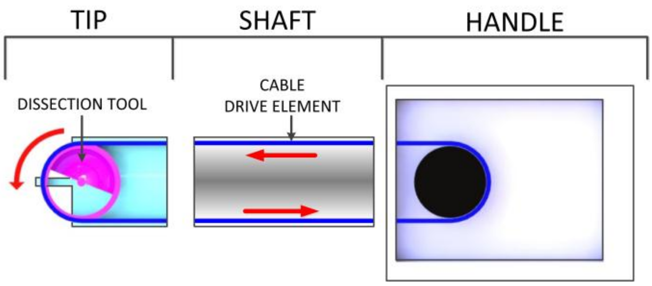


Fig. 12: Final conceptual morcellator design. The red arrows indicate the direction of motion of the resection tool and drive element. The black circle indicates the drive axle of the morcellator.

G. *Final Morcellator Design*

In the previous sections the different requirements to which the morcellator should comply were discussed in phases, finally leading to the conceptual morcellator design. In Fig. 13 the different requirements are graphically represented to get a clear overview. The main design requirements (as illustrated in Fig. 13) form the design ‘skeleton’ to which the morcellator should comply. To achieve a fully functional morcellator, additional design elements should be taken into consideration, including the clinical setting in which the morcellator will be operated and manufacturability.

The choice for a disposable, reusable or even a ‘resposable’, i.e. partly reusable and partly disposable, morcellator has multiple consequences for the final design of the morcellator. A disposable instrument will need to be easily manufactured and does not need to be cleaned and sterilized after use, whereas a reusable instrument can be more complex but does need to be cleaned and sterilized. The choice for a ‘resposable’ morcellator will allow for more freedom in design. The choice is made to design the morcellator in such a way that it is possible to disassemble, clean and sterilize the parts individually, making reuse of the morcellator an option. Regarding to instrument functionality, the morcellator will be designed as a handheld instrument, which can be directly operated by the surgeon using one or two hands. The handpiece will incorporate a drive axle for the connection of an external actuator, a cable tensioning mechanism, an aspiration chamber for contact initiation and tissue transportation and aspiration connection nipple for the connection of a vacuum pump and tissue container.

The design requirements as illustrated in Fig. 13 as well as the above mentioned additional requirements are translated towards a functional morcellator design. The final rigid tip design of the morcellator only incorporates 3 functional elements:

(1) Radial rotating cylindrical resection tool
(2) Static rigid tip element
(3) Connection piece

In Fig. 14 this tip design is schematically illustrated. The overview of the final design is schematically illustrated in Fig. 15, consisting of 28 functional parts most of which are situated in the handle piece.

In the original concept of the morcellator the radial rotating resection tool was spherical in design. However, to improve manufacturability and keep manufacturing costs low, the spherical design is changed towards an easier to manufacture design. In accordance, the rigid tip of the morcellator is executed as a filleted square column (width 5 mm, wall-thickness 0.3 mm) instead of cylindrical in shape. Furthermore, the manufacturing of the arc situated at the distal tip of the morcellator that provides the reaction force during resection proved too difficult to manufacture. It was therefore decided to omit this feature and to incorporate the second cutting edge inside the rigid tip of the morcellator. To keep the frontal cutting action intact, the resection tool was fitted with serrated teeth to grip the tissue and subsequently fully dissect it at the second cutting edge of the morcellator.

The manufacturing of a continuous cable drive element, as indicated in Fig. 12, also proved difficult, with it breaking near the weld in the heat-affected zone (HAZ) due to work hardening, so it was decided to use a pulley mechanism, as illustrated in Fig. 15. One cable end of the drive cable will be connected to a pulley, the other to a mass that will deliver the needed tension force on the cable. The cable is rotated around the pulley multiple times before being guided towards the resection tool and guide cylinder that changes the direction of the cable and will allow for using the mass and thus gravity for cable tensioning. An additional advantage of this mechanism being that the cable tensioning can be easily controlled by changing the mass.

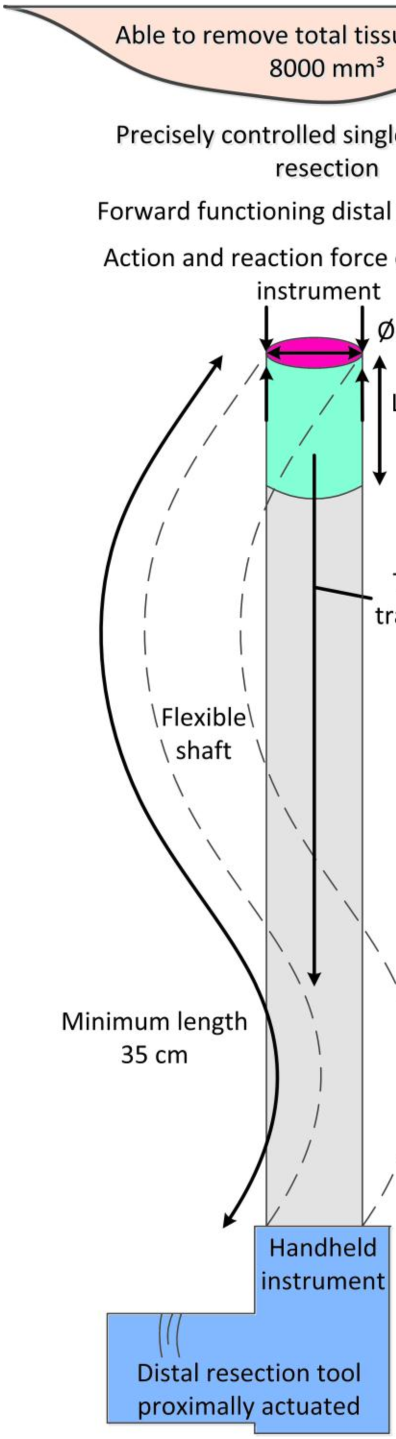


Fig. 13: Graphical representation of the design requirements discussed in the previous sections.

The radial rotating cylindrical resection tool (Ø = 4 mm, width = 4.4 mm) incorporates multiple cutting edges to achieve two main goals; deliver the needed action force during resection and provide the force to draw the tissue towards the second cutting edge of the morcellator incorporated inside the static rigid tip element. The design allows for unidirectional resection in two opposing directions. The axial translating flexible cable (Ø = 0.3 mm) is situated in

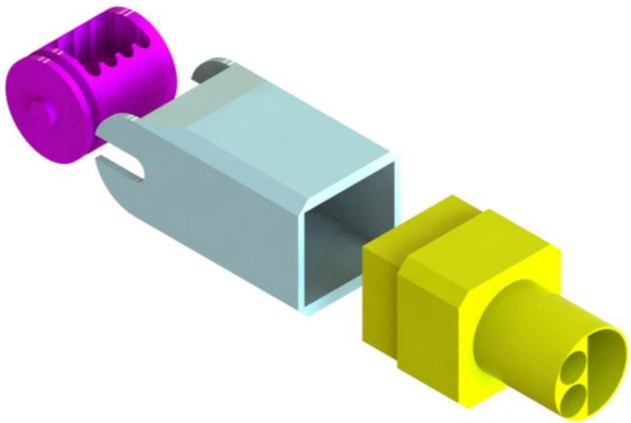


Fig. 14: The tip of the morcellator. From left to right: resection tool, static rigid tip element, and connection piece.

a trapezoid slot incorporated in the resection tool. The trapezoid slot provides a high surface area between the cable and the slot and more importantly has an automatic tightening effect on the cable increasing the friction force and thus the efficiency of the energy transference. Motion transference from the axial translating motion of the cable drive element to the needed radial rotation motion of the resection tool is achieved by simple cylindrical transmission hinges (Ø = 1 mm) and guide slots in the static rigid tip element. These hinges are directly linked to the resection tool, minimizing the instrument complexity.

The static rigid tip of the morcellator is connected to the flexible shaft ($Ø_{outer}$ = 5 mm, 1 mm wall-thickness, l = 35 cm) by means of a connection piece. This connection piece provides two main functions; the connection between the tip and the shaft of the morcellator, and a guidance structure to the two springs that envelop the cable drive mechanism. These two springs will prevent kinking of the morcellator during operation by absorbing the forces of the cable drive mechanism on the flexible shaft and will protect the flexible shaft from damage potentially inflicted by the cable drive element. The design of the drive element provides sufficient room for a central tissue transportation channel incorporated inside the flexible shaft. This tissue transportation channel allows for pieces with up to 1 mm in diameter to be transported from the distal end of the morcellator towards the proximal end by means of aspiration.

Connecting the flexible shaft to the handle of the morcellator is another connection piece, which also incorporates two holes in which the springs are inserted and fixed. Inside the handle a bearing house is inserted that incorporates two bearings, the drive axis, pulley, and guide cylinder. The tension spring that is situated between the handle housing and the bearing housing is used for cable tensioning and bearing housing fixation in the handle piece.

Aspiration is achieved by sealing off the handle piece by using a lid which partly falls into the handle piece and a rubber ring which seals of the entry hole of the drive axis. Finally, a vacuum pump can be connected to the back of the handle piece.

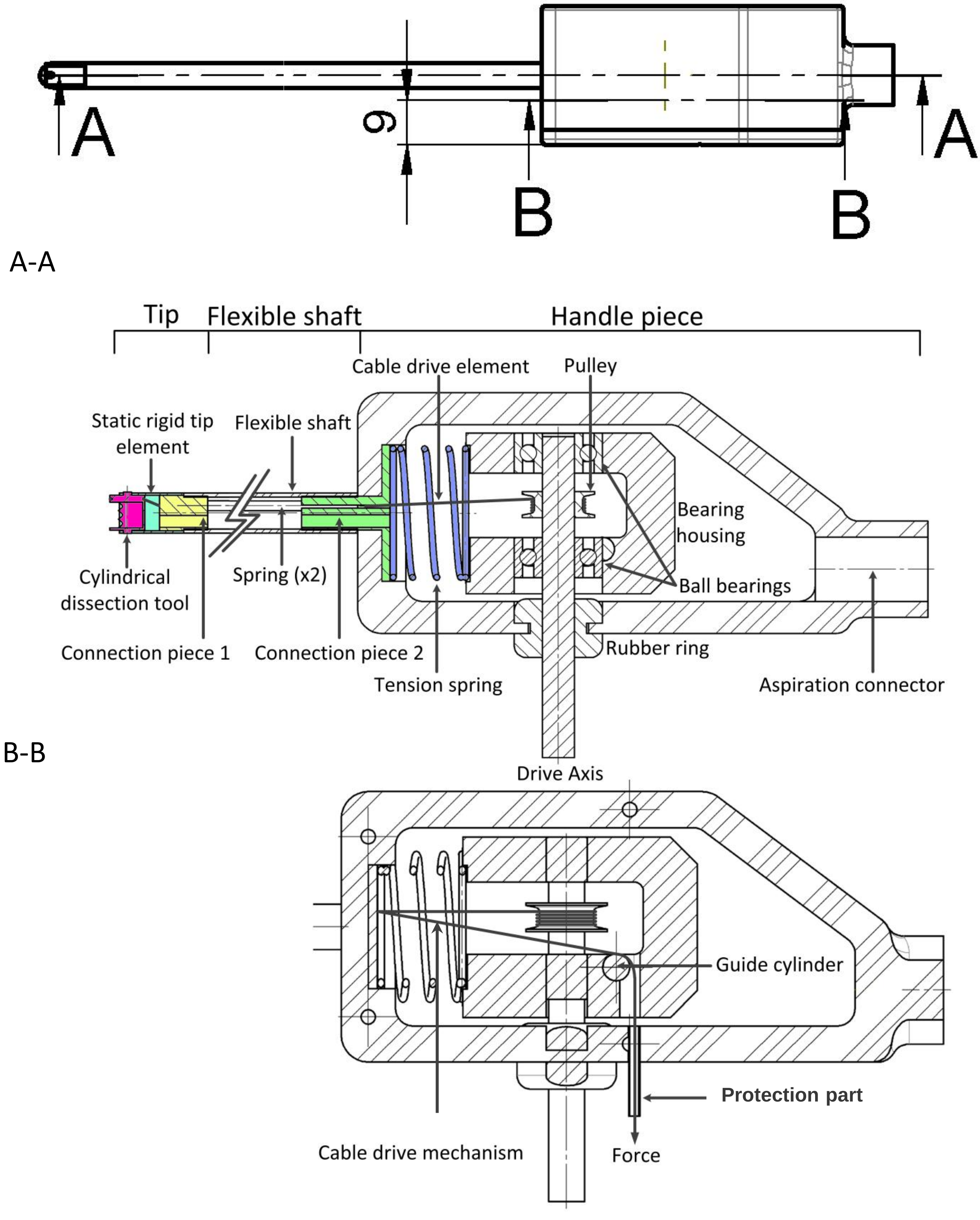


Fig. 15: Schematic representation of the final design. Above: Top view of the HORSE morcellator. Middle: Section A-A representing a median cross-section of the HORSE morcellator. Below: Section B-B representing a cross-section 9 mm from the indicated axis to visualize the cable drive mechanism of the HORSE morcellator.

IV. PROTOTYPE AND EXPERIMENT

A. *Prototype Development*

The prototype, also called the HORSE morcellator, served as a validation model for the flexible morcellator concept. The main goals of the prototype were threefold; 1) validating the endovascular approach for the surgical treatment of Cushing's disease in horses, 2) validating the working principle of the flexible cable drive mechanism, and 3) validating the working principle of the radial rotating cylindrical resection tool in combination with the aspiration system. For validating these working principles, the prototype was tested in-vivo, as will be discussed in the next Chapter.

In Fig. 16 the 28 functional parts of the HORSE morcellator are illustrated. From these 28 functional parts of the morcellator, only 10 parts needed to be manufactured. The remaining parts were off the shelf available (cable, (Allen) screws, tension spring, bearings, weights and rubber ring), were ordered (silicone rubber flexible shaft) and, were retrieved from an old endoscope (two springs inside the flexible shaft). For the manufacturing of the remaining 10 parts, multiple construction materials were used. The tip of the morcellator, i.e. resection tool and rigid tip, was constructed out of High-Speed Steel (HSS), which is a common alloy used in tool bits and cutting tools. HSS allows for reuse of the resection tool without the loss of sharpness of both the serrated teeth of the resection tool and cutting edge of the rigid tip. The flexible shaft of the morcellator was constructed out of polysiloxane. Polysiloxane is a common construction material for long-term (over 30 days) vascular catheters and is suppler than polyethylene (PE), polyvinyl chloride (PVC), and polytetrafluorethylene (PTFE), used for short-term vascular catheters [25]. Finally, the drive axle of the HORSE morcellator was constructed out of stainless steel; the connection pieces and bearing housing out of aluminum.

Size restrictions and the choice for HSS required the use of wire-cut Electric Discharge Machining (EDM) for the manufacturing of the cylindrical resection tool, static rigid tip element, the two connection pieces and the guide cylinder. This technique allowed for high-precision manufacturing and prevented distortion of the small parts due to the lack of contact between the machining tool and the parts. The handle piece, consisting of two parts; the handle and the lid, of the morcellator were manufactured out of a rigid polymer using rapid prototyping, since high precision or strength of this piece was not necessary. Finally, for the manufacturing of the bearing housing, protection cylinder and the pulley, a conventional CNC machine was used.

The exploded view of the tip of the prototype is illustrated in Fig. 17. After assembly the overall length of the tip was measured at 17 mm, allowing for passive steering through the vascular system. In Fig. 18 the assembled tip is illustrated together with a standard size match, to indicate the size of the tip. Finally, a close-up view of the handle piece of the HORSE morcellator prototype is illustrated in Fig. 19.

The actuation of the morcellator is performed by a drilling machine (Makita 6271 DWAE) with speed control between 0 to 1300 rpm. In comparison, current morcellator designs use a rotational speed between 100 and 1000 rpm for morcellator [21]. From one morcellator the rated torque was found at 0.5 Nm [21]. From this data the output power range to which the electromotor should comply was calculated to be between 6 and 60 W. The drilling machine can deliver up to 165 W of output power, which should be more than sufficient.

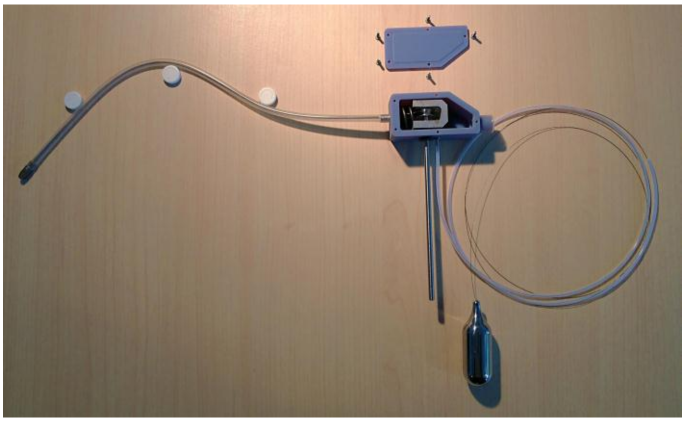


Fig. 16: The HORSE morcellator illustrating the 28 functional parts of the morcellator.

Fig. 17: Final tip of the morcellator prototype. From left to right: radial rotating resection tool, rigid tip element, connection piece 1.

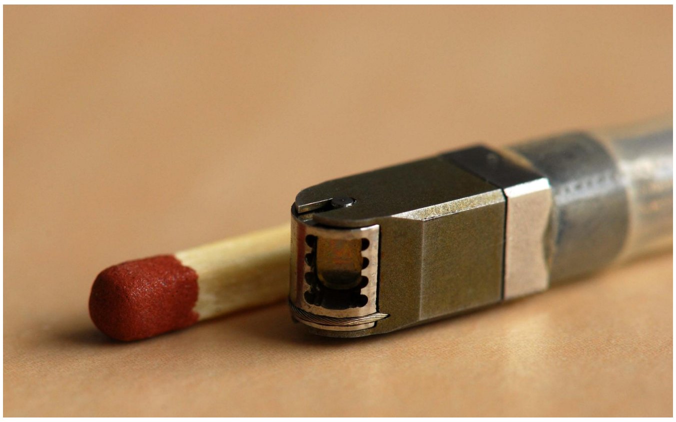


Fig. 18: Assembled tip of the HORSE morcellator prototype.

The aspiration system of the morcellator consists of 6 functional parts; the main components being a tissue container and vacuum pump. The tissue container will be used as storage container for the morcellator tissue and will prevent tissue contact with the vacuum pump. Two swivels (9 and 13 mm) connected to this tissue container in combination with two tubes (Ø 9 and 13 mm) will connect the morcellator and vacuum pump to this container and will complete the aspiration system. In Fig. 20 the aspiration system is illustrated.

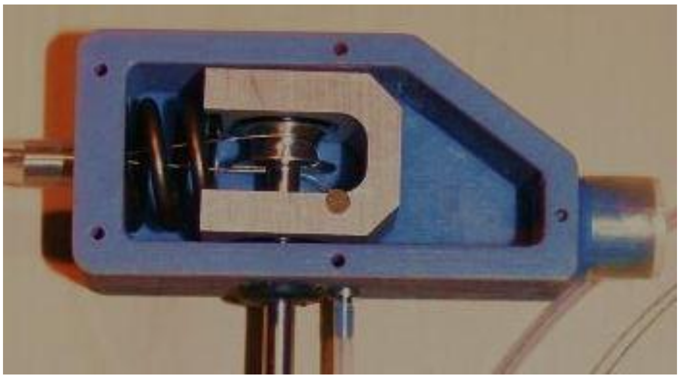


Fig. 19: Handle piece of the HORSE morcellator prototype.

Fig. 20: Aspiration system. From left to right: vacuum pump (pink), connection tube vacuum pump to tissue container, swivel 9 mm, tissue container, swivel 13 mm, and connection tube tissue container to HORSE morcellator.

B. Prototype Assembly

The assembly of the prototype entailed multiple consecutive steps and tools. The first step in the assembly process required the use of a laser welding machine. This machine was used to assemble the connection piece to the two springs (that envelop the cable drive element). After finishing this process, both the static rigid tip element and silicone tube are slid over the opposite sides of the connection piece. On the opposite end of the silicone tube, the second connection piece is positioned inside the handle. The two enveloping springs are positioned and locked into place inside this connection piece, allowing these springs to absorb the forces during resection. Finally, the resection tool is positioned loosely into place inside the static rigid tip element to complete the flexible shaft assembly of the morcellator.

For actuating the morcellator, the correct assembly of the cable drive element mechanism and handle piece is of great importance. First, the cable drive element needs to be guided through the two springs, positioned in the trapezoid slot of the resection tool and finally guided through the tension spring. One cable end needs to be fastened with two Allen screws to the pulley, while the other cable end is guided towards the guide cylinder, through the bearing housing and protection part (previously screwed into the handle piece) to the outside of the handle piece where it is connected to an adjustable mass, providing cable tensioning. To tension the entire system and keep the bearing housing in place in the handle piece, the tension spring is positioned inside a recess inside the handle piece of the morcellator (over the cable drive element). The guide cylinder is inserted inside the bearing housing, which is subsequently press fitted with two roller bearings and positioned inside the handle piece with the tension spring being locked into place by a round recess in this housing and the handle piece. The pulley is positioned inside the bearing housing, after which the drive axis is guided through the drive axis hole in the handle piece and positioned into the bearing housing roller bearing construction. The pulley is then fastened to the drive axis by using a small Allen screw. The incorporation of a flat side to the drive axis will prevent the pulley from turning independently from the drive axis. Finally, the cable is rotated around the pulley multiple times and the actuator is fixated to the drive axis by means of a compression fitting.

The final steps of the total assembly process will focus on obtaining sufficient aspiration for contact initiation and tissue transportation. The handle piece will function as a large aspiration chamber, and as such will be closed by using five M2 flathead screws. The lid is designed that it will partly fall into and seal off the handle piece. A rubber ring will be used to seal off the hole around the drive axis. The vacuum pump will be assembled and connected to the morcellator. For this purpose, a 13 mm tube will be connected to the back of the handle piece, where a specially designed cylindrical connector is situated. This tube is guided towards the tissue container where it is connected with a swivel to obtain an airtight seal. Another swivel connects the tissue container to the vacuum pump by means of a second tube (Ø 9 mm). The connection of the vacuum pump to a power outlet completes the aspiration assembly and thus the total assembly process. In Fig. 21 the final assembled prototype is illustrated and in Fig. 22 the total morcellation set-up is illustrated including the aspiration and actuation.

C. Proof of Principle Experiment

The HORSE morcellator was tested at the University of Technology Delft and the Faculty of Veterinary Medicine of the University Utrecht. The morcellator was tested for the validation of the following properties:

- The endovascular approach to reach the pituitary gland in a horse;
- The flexible drive element mechanism;
- The resection tool design in combination with the used aspiration system.

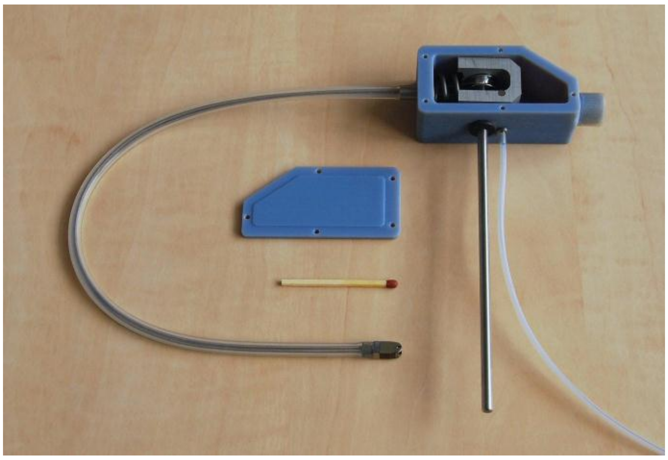


Fig. 21: Assembled HORSE morcellator prototype.

Fig. 22: Total HORSE morcellator assembly including actuator and aspiration system.

For the cadaver tests, one horse head cadaver was used. The head was drained of blood and cut in two identical median sections for visualization of the pituitary gland. After positioning the horse head cadaver on an adjustable table, an incision was made to expose the facial vein. The morcellator prototype was connected to the actuator and tissue container, which was subsequently connected to the vacuum pump. To determine the required cable tensioning for smooth motion transference from the cable to the resection tool, the cable was tensioned with an adjustable mass until smooth energy transfer was illustrated. The cable drive element was then tensioned by connecting the required mass on the cable end and positioning the mass to hang freely from the side of the table.

By inserting the HORSE morcellator into the facial vein and subsequently gently pushing the morcellator through the vascular system, the morcellator was guided towards the pituitary gland. After visual confirmation of the correct positioning of the morcellator near the pituitary gland, the vacuum pump was turned on to achieve contact between the resection tool and the pituitary tissue. After achieving full tissue contact the actuator was turned on, which in turn started the resection process as well as the tissue transportation process. In Fig. 23 the test set-up is schematically illustrated.

During the morcellation process, a HD video camera was used for the recording of the resection and transportation process. This video was later used for the determination of the rotational speed of the morcellator during resection.

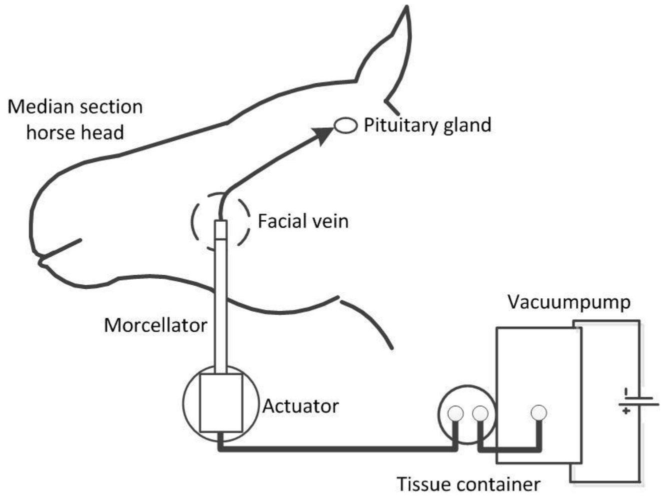


Fig. 23: Schematic illustration of test set-up during experiment.

D. Results

The working principle of the HORSE morcellator prototype was tested at the Faculty of Veterinary Medicine in Utrecht. After exposing and making an entry point in the facial vein, the HORSE morcellator was successfully inserted in this vein. The insertion of the HORSE morcellator inside the facial vein of the horse head cadaver is illustrated in Fig. 24. The HORSE morcellator was able to passively steer through the vascular system with relative ease. By following the procedure illustrated in Fig. 3, the HORSE morcellator was able to reach the pituitary gland as is illustrated in Fig. 25. Once positioned near the pituitary gland the HORSE morcellator was able to remove tissue from the pituitary gland by actuating the resection tool. No slip was observed between the cable and the resection tool using 3 N of wire tensioning and the cable drive mechanism did not kink or bend the cable during actuation; validating the overall working mechanism of the cable drive element in combination with the two absorbing springs. The resection tool was capable of resection in the clockwise and counterclockwise direction by reversing the direction of the actuator and the double cutting edges of the resection tool and rigid tip. From data retrieved from video capturing during resection, the average rotational speed of the resection tool was measured at 75 rpm.

In combination with the resection tool, the aspiration system was capable of initiation contact between the resection tool and pituitary tissue. Directly following resection, the dissected tissue was transported along the transportation lumen as is illustrated in Fig. 26. The design of the resection tool caused a periodical variation in the aspiration force on the tissue; from zero with a closed resection tool to a normal distribution with an open resection tool. The closed resection tool state did not cause the collapse of the flexible silicone shaft. Furthermore, the resection tool served as a tissue container during resection, guiding the tissue towards the second cutting edge at the rigid tip of the instrument and subsequently transporting it towards the tissue transportation lumen for tissue transportation towards the proximal end of the morcellator.

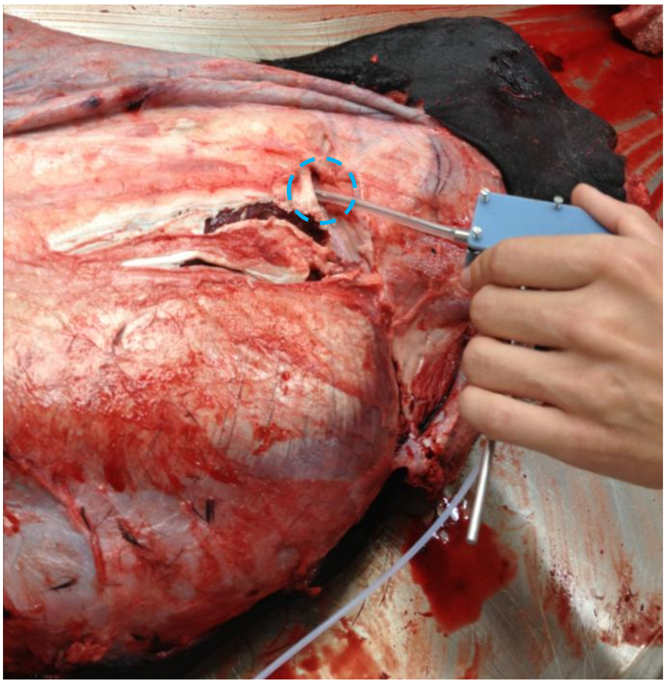


Fig. 24: Median section of horse head cadaver (nose directed towards the right) with the HORSE morcellator prototype inserted in the facial vein.

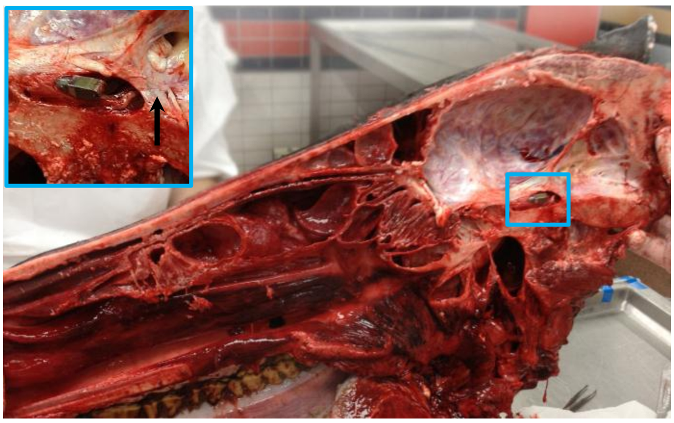


Fig. 25: Median section horse head cadaver with HORSE morcellator prototype inserted and positioned at the pituitary gland. The arrow indicates the normal position of the pituitary gland (not shown on the photo).

Fig. 26: Section of the HORSE morcellator transportation lumen with the aspirated tissue inside the flexible shaft.

V. DISCUSSION

The successful proof of principle experiment of the HORSE morcellator and the endovascular approach has made the surgical treatment of Cushing’s disease in horses a real possibility in the near future. The HORSE morcellator has illustrated the ability to reach the pituitary gland by using the facial vein, as illustrated in Figures 24 and 25. Passive steering through the vascular system was relatively easy to achieve without visible damage to the vascular system. Pituitary tissue was dissected from the surrounding tissue and subsequently transported towards the proximal end of the morcellator.

During testing the working principles of the cable drive element, aspiration system, and resection tool design were validated. The cable drive element was capable of actuating the resection tool without kinking the flexible shaft and most importantly while still remaining flexible. The friction force between the cable and the trapezoid slot proved sufficient in providing smooth transition of the axial translating cable drive element to the radial rotating resection tool without the use of high cable tensioning (3 N). An additional advantage of the self-tightening effect of the trapezoid slot included the prevention of the cable drive element from sliding out of the slot. In combination with the smooth motion transference of the cable drive element, the aspiration system was able to provide contact initiation and tissue transportation along the flexible shaft of the morcellator. Furthermore, the resection tool provided sufficient grip on the tissue to guide the tissue towards the second cutting edge of the morcellator (located at the rigid tip of the morcellator). This feature allowed for resection in the frontal and sideways direction. The use of HSS allowed for reuse of the resection tool and rigid tip without apparent loss of sharpness. Furthermore, the ability of the morcellator to dissect both in the clockwise as counterclockwise direction also offered considerable advantages since it allowed for the resection of pituitary tissue from either side of the tip of the morcellator.

Further development of the current HORSE morcellator for the surgical treatment of Cushing’s disease in horses in a clinical setting is a feasible next step in developing a new surgical treatment modality for the treatment of Cushing’s disease in horses. However, to achieve a fully functional instrument that can be used in clinical practice, redesign will need to be considered.

Even though the HORSE morcellator prototype is considered fully functional in terms of performing the main tasks of the morcellator, i.e. flexible actuation, resection and tissue transportation, there are some important redesign points that should be taken into consideration for a possible second version. First of all, the prototype experienced some difficulties with the pulley mechanism. The cable tended to wind around the drive axis and become tangled as a result. The main reason for this being: the size of the pulley, which was too small for the length of the cable, and the position of the pulley, located higher than the connection piece which guides the cable. Therefore, redesign of the pulley is necessary to prevent this from happening. Next to or in combination with the pulley redesign it is also necessary to improve the entire drive/tensioning mechanism of the cable drive element. During morcellation it was proven difficult to keep the cable properly tensioned since the cable length was longer than the table was high. Furthermore, in a clinical setting it is not feasible to use a weight for cable tensioning. A new handle piece should therefore be designed that incorporates both the actuator and the cable drive/tensioning mechanism. Tissue contact with the drive mechanism inside the handle piece should be prevented by designing a separate aspiration lumen.

In addition to the redesign points mentioned above, it is necessary that for the clinical application of the morcellator the biocompatibility, cleanability and sterilizability are taken into account. In the current prototype the flexible shaft and absorbing springs are made out of the biocompatible materials silicone rubber and stainless steel respectively. However, the cable and connection pieces are made out of non-biocompatible stainless steel and aluminum respectively. Since these parts come into direct contact with the tissue, these parts should be made out of biocompatible materials in the redesigned prototype. Furthermore, even though, HSS does not contain any know toxic elements and is similar in composition to multiple biocompatible metals, HSS is not a proven biocompatible material, making further tests that prove the biocompatibility a necessity. In respect to the cleanability of the morcellator, this prototype proved to be relatively easy cleanable since all parts, besides from the two springs connected to the connection piece at the tip of the morcellator, could be disassembled and thus properly cleaned separately. The use of silicone rubber for the flexible shaft also makes it possible to sterilize the prototype under high temperatures.

Finally, to achieve a truly functional and clinical applicable morcellator the following additions to the current design should be made. To get a clear view of the operation area the use of an optic fiber or other means for visualization, like a small camera, of the pituitary gland is a must. This will allow for confirmation of the right positioning and give feedback during resection. In combination with the visualization of the positioning of the morcellator, the addition of at least 1 active DOF tip motion will increase the chance of successful removal of the entire pituitary tumor or gland. Additionally, adding at least one active steerable DOF, will allow for easier navigation to the pituitary gland and potential other sites in the horse head.

Next to the development of the HORSE morcellator, the endovascular approach and the implications of this should be considered. Since as of today no surgical approach has ever been attempted, the post-surgical results are still unclear. The chance of post-removal bleeding is present as well as the potential damage to the surrounding structures of the pituitary gland. Furthermore, the presence of the HORSE morcellator in the vascular system may potentially cause damage to the vascular system and oxygen deprivation somewhere along the vascular route to the pituitary gland. Since the cross-section of the tip of the HORSE morcellator is square in shape, the chance of damage to the vascular system is somewhat higher than that of a circular cross-section. However, this shape does prevent the total blockage of the vessel, due to the imperfect fit of the instrument inside the vessel. Therefore, redesign of this tip should take both into account. Additionally, the use of aspiration for contact initiation will cause blood to be aspirated towards the proximal end of the morcellator, potentially causing blood loss in the surgical area near the pituitary gland.

The determination of the potential risks, complications and surgical outcome of the used endovascular approach in combination with the HORSE morcellator, will require a lot more testing of this procedure. This testing will give answers to the questions raised and above all will help guide the redesign process of the HORSE morcellator.

Even though the HORSE morcellator is designed with the horse in mind, the surgical treatment of Cushing's disease and other pituitary disorders in humans can also potentially improve by the development of this flexible HORSE morcellator. Even with the current surgical approaches and tools not every tumour can be reached or removed. A flexible instrument that can improve this reachability can potentially aid in improving the surgical outcome. However, for the HORSE morcellator to be applied for endovascular pituitary resection, downscaling of the HORSE morcellator towards 1-2 mm diameter instrument is a necessity. Downscaling of the HORSE morcellator will require the need for an even smaller diameter drive cable, increasing the chance of failure, and resection tool design. Even though wire-EDM can manufacture up to 0.05 mm holes, manufacturing at this size is difficult and can significantly increase the manufacturing costs. By abandoning the idea of endovascular surgery in humans, the downscaling of the HORSE morcellator can be brought back to about the 3-4 mm diameter range. At this size the regular entry points in human pituitary surgery, like the nasal cavity or palate, can be used for the insertion of the HORSE morcellator. Furthermore, the flexible design of the HORSE morcellator can potentially lead to the development of a new surgical approach in humans.

Next to the prospect of the HORSE morcellator in pituitary surgery in humans and horses, the HORSE morcellator can potentially be used in other surgical fields and/or animals as well. In terms of animals; dogs, cats, donkeys and monkeys are known to suffer from Cushing's disease, making them candidates for the surgical removal of the adenomas with the HORSE morcellator. In terms of potential surgical fields; current morcellators are most commonly used for applications in the abdomen. These devices are all rigid and are therefore limited in terms of DOF and thus reachability. By designing the HORSE morcellator to be steerable and flexible, the reachability can be improved significantly. Other well-suited applications for the HORSE morcellator may be found in the removal of tumors in the urinal and gastrointestinal tract. The HORSE morcellator can be guided by the urethra, bowel, and esophagus, offering passive steerability options, towards the tumor where tumor resection can commence.

To get an idea of a potential design of the HORSE morcellator in the near future, in Fig. 27 the future vision of the HORSE morcellator is illustrated. The HORSE morcellator will contain a handle piece with an integrated actuator, tensioning mechanism and aspiration system. Furthermore, the tip will be actively steerable in at least 2 degrees of freedom by using the joystick integrated in the handle piece. The rigid tip of the instrument will be cylindrical in shape containing a spherical resection tool. A special recess in the tip allows for the integration of an optical fiber or small camera for visualization of the operation area. All the parts will be made out of biocompatible materials and are able to undergo cleaning and sterilization. The HORSE morcellator will be partly disposable, with a flexible shaft and tip that can be disposed after several surgeries, and partly reusable, with a handle piece that can be reused for longer periods of time. Downscaling of the design to a 3 mm diameter flexible shaft will allow for the morcellator to be utilized in human surgery and other medical applications; broadening the possibilities of the design.

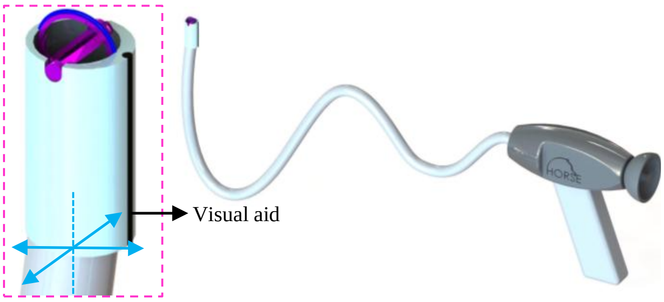


Fig. 27: Future vision of the HORSE morcellator after redesign. The blue arrows indicate the active steerable degrees of freedom of the tip of the morcellator. The integration of the optical fiber or other visual aid in the tip of the morcellator is indicated in black. The resection tool is indicated in pink, the cable drive element in blue and the rigid tip of the morcellator in light green.

VI. CONCLUSION

The systematic approach of the design process has led to the development of a prototype for the surgical treatment of Cushing’s disease in horses. By subdivision of current morcellator design into categories corresponding to the fundamental differences, design gaps were found and translated into design opportunities. These design opportunities were subsequently translated into the final morcellator design and prototype. The final HORSE morcellator prototype has an innovative flexible cable drive mechanism and resection tool design that is currently not seen in any other clinically applied morcellator. Redesign is necessary to obtain a truly functional clinical applicable instrument; an instrument that can be applied in a clinical setting to surgically treat Cushing’s disease in horses and maybe in the future, humans as well. However, the prototype has illustrated the feasibility of the endovascular approach for the surgical treatment of Cushing’s disease in horses, making the surgical treatment of horses in normal veterinary practice a real possibility in the near future.

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A Comprehensive Overview of Removal Methods for the Surgical Treatment of Cushing's Disease for Human and Veterinary Applications

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1 Background

Over the last few decades the prevalence of equine Cushing's disease has been increasing. Surgical treatment of this disease, which entails the removal of the pituitary (pars intermedia) adenoma located within the sella turcica of the skull (a saddle-shaped depression in the sphenoid bone), can be performed on humans. Yet, due to anatomical constraints, the same procedure is not applicable to horses. As a result, the only available treatment modality to date is oral medication, which most horse owners are unable to afford. Additionally, oral medication only offers a temporary solution to the disease, with varying outcomes [1].

New ways to surgically treat equine Cushing's disease is a necessity to provide a more cost effective treatment for the horse owners. Furthermore, insight into new treatment modalities to halt disease progression and potentially aid in surgical treatment are warranted from a comparative medicine perspective. Additionally, better understanding of equine Cushing's disease could provide insight into new treatment modalities for human Cushing's disease as well as potentially help unravel the early initiating event in the disease development.

The aim of the current study was to provide a comprehensive overview of potential removal methods for the surgical treatment of Cushing's disease in both horses and humans.

2 Methods

To determine the feasibility of surgical treatment of equine Cushing's disease, the anatomical similarities and differences between the equine and human brain and head were studied. The standard surgical procedures performed in humans, i.e. transcranial, transnasal and transseptal pituitary surgery, were taken as a point of departure in this paper to find approaches that are hypothetically suitable for equine surgical treatment.

After determining the most suitable surgical approach in horses, a search area was defined to determine possible treatment options. In order to obtain a complete and comprehensive overview of all the suitable tissue removal techniques for equine pituitary surgery that are currently applied in humans, a literature search has been performed in the database of Web of Knowledge. The keywords used for the literature search were subdivided into four categories. The following terms were used:

- **Medical field:** Minimally invasive, catheter, laparoscopic and endoscopic.
- **Tissue removal method:** Cut, remove, harvest, debulk, morcellate, aspirate, ablate and fragmentate.
- **Tissue type:** Tumor, pituitary, hypophysis, adenoma, myoma, polyps, abdominal and graft.
- **Instrumentation:** Technique, device and instrument.

Multiple sequential searches were executed. The results where scanned for relevancy and subsequently in- or excluded from this literature survey. Tissue removal methods that necessitate multiple simultaneous or sequential instrument insertions or have been specifically designed for the removal of dense tissues (such as bone) were considered outside the scope of this literature survey.

3 Results

After examining the similarities and difference between the horse and human brain, it becomes clear that surgical treatment of equine Cushing's disease can be a realistic treatment modality. The key difference between humans and equines lies in the shape of the skull; the equine skull is more elongated than the human skull and is generally much thicker (see Fig. 1). This renders it more difficult to surgically treat equine Cushing's disease via the transseptal, transnasal or transcranial approach where multiple bony walls have to be traversed.

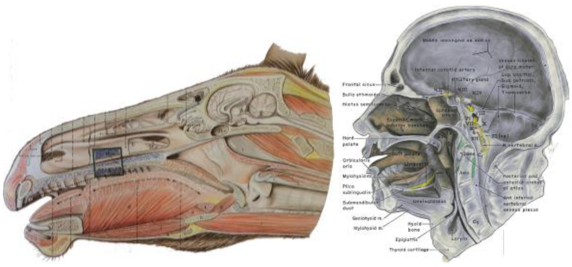

Fig. 1: Left: median section of the equine head. Right: median section of the human head [2;3].

However, unlike in humans, multiple superficial veins, like the facial vein, provide access to the deep facial vein, vena reflexa, ophthalmic vein, and finally the intercavernous sinus; the outflow duct of the pituitary gland. With a maximum diameter of 10 mm, these veins can be used to gain direct contact with the pituitary gland without the need to traverse multiple bony walls. Therefore, the use of a catheter, disposed through the vascular system, to approach the equine pituitary gland is a realistic treatment option.

Executing the literature search has resulted in the identification of fourteen feasible tissue removal techniques.

The removal methods are subdivided into two categories: ‘division’ and ‘conversion’. The ‘division’ category encompasses all the methods that dissect the tissue without converting it. This category is further subdivided into ‘piecewise removal’, i.e. removal of palpable pieces of tissue (≥ 5 mm^3), and ‘debulking removal’, i.e. removal of tissue in less than palpable pieces of tissue (< 5 mm^3). The category ‘conversion’ is made up of methods that remove tissue by converting it into another state. In Fig. 2 the different categories and the accompanying removal methods are illustrated.

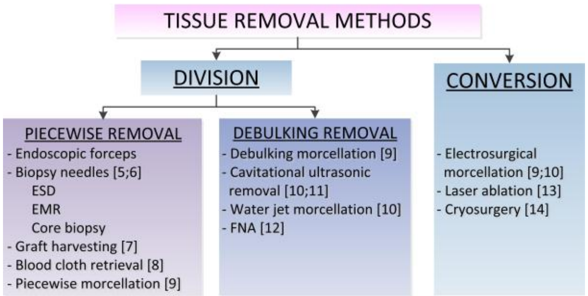

Fig. 2: Schematic overview of tissue removal methods. ESD: endoscopic submucosal resection, EMR: endoscopic mucosal resection and FNA: fine needle aspiration.

4 Interpretation

The use of the vascular system in the equine head is a realistic option due to the large diameter veins that are in direct contact with the pituitary gland, whereas in humans the pituitary gland is not easily accessible via the veins due to the smaller diameter and structure. However, the vascular system as entry point to the equine pituitary gland puts considerable constraints on the removal method. First of all, the removal method must be able to be integrated into a flexible catheter which can reach the surgical site; requiring a minimal stiff tip length to accommodate the minimum bending radius of the vascular system. Secondly, the removal method has to fit inside a catheter of a maximum diameter of 5 mm and possibly smaller with future human patients in mind.

Multiple catheter insertions are not desirable due to the increased risk of blood loss and damage to the veins. Therefore, removal methods that completely dissect the tissue from the surrounding tissue (cyclic resection) are preferred over methods that necessitate the use of another tool to dissect the tissue from the surrounding tissue (continuous resection).

The position and structure of the equine pituitary gland also puts considerable constraints on the removal method. Multiple large blood vessels, nerves and delicate brain tissue lie dorsally to the pituitary gland. Damage to these structures can possibly lead to severe complications. Preference is therefore given to a removal method with high tissue selectivity and precision that is easily controlled in the axial direction and has the option to coagulate vessels.

The conformance of the removal methods to the requirements mentioned above is illustrated in Table 1. Multiple techniques are considered feasible options for pituitary gland removal. However, further research is necessary to determine the most suitable removal method.

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Table 5: Overview of the removal methods including compliance with respect to various requirements.

Removal method	Catheter integration	Removal process	High precision resection	Tissue selectivity/ Coagulation option	OF NOTE	Currently applied for:
Endoscopic forceps	Feasible	Cyclic	No	No/Feasible	The hinge action requires additional space.	Handling and removal of soft tissue.
Biopsy needles [5;6]						
- ESD	Feasible	Cyclic	No	No/Yes	Many different steps.	Gastrointestinal tumor resection.
- EMR	Feasible	Cyclic	No	No/Yes	Many different steps.	Gastrointestinal tumor resection.
- Core biopsy		Cyclic	Feasible	No/Feasible	Debulking morcellation.	Suspicious soft tissue biopsy.
Graft harvesting [7]	Difficult	Cyclic	No	No/Yes	Complex tool.	Nerve and vessel harvesting.
Blood clot retrievers [8]	Yes	Cyclic	No	No/Feasible	Shape memory effect cannot be controlled.	Endovascular thrombectomy.
Piecewise morcellation [9]	Feasible	Continuous	Feasible	No/Feasible	Fast removal method. Finite removal in COOK HSEL.	Hysterectomy, Nephrectomy, Myomectomy, Prostatectomy, Splenectomy.
Debulking morcellation [9]	Feasible	Cyclic	Feasible	No/Feasible	Fast removal method.	See piecewise morcellation.
CUSA [10;11]	Difficult	Cyclic	Yes	Yes/Yes	Complex tool.	Removal of neoplasms of the CNS (among others).
Water jet morcellation [10]	Yes	Cyclic	Yes	Yes/Yes	Axial direction difficult to control.	Liver and kidney resection. Urology.
FNA [12]	Feasible	Continuous	Yes	No/No	Only for incoherent tissue.	Suspicious soft tissue biopsy.
Electrosurgical morcellation [9;10]	Feasible	Continuous	Feasible	No/Yes	Dangerous near brain.	Not in clinical use.
Laser ablation (ELANA) [13]	Yes	Cyclic	Yes	Yes/Yes	Axial direction difficult to control.	Neurology: bypass surgery in the brain.
Cryosurgery [14]	Feasible	Cyclic	Yes	Yes/Yes	Axial direction difficult to control.	Treatment of hemangiomas, spinal cord tumors and hyperplasia.

ESD: Endoscopic Submucosal Resection, EMR: Endoscopic Mucosal Resection, CUSA: Cavitational Ultrasonic Surgical Aspirator, ELANA: Excimer Laser Assisted Non-occlusive Anastomosis, CNS: Central Nervous System.

APPENDIX B: MORCELLATION METHODS

A.1. Single-sided Axial Cutting

No mechanical morcellators utilizing single sided axial cutting for soft tissue purposes are found in literature. However, there are some examples of medical devices that use single sided axial cutting:

- Bio-inspired spring-loaded biopsy harvester [26];
- Auto Suture Visiport [27].

These instruments both contain a translating single sided axial cutting blade to dissect tissue. The Bio-inspired spring-loaded biopsy harvester is used for biopsy purposes. The device uses a spring to load a cutter shaped like a crown, as illustrated in Fig. 28. After releasing the tension on the spring, the cutter is translated into the lesion where it subsequently collapses to a cone shape.

Fig. 28: Spring-loaded biopsy harvester [26].

The Auto Suture Visiport (Covidien) is an instrument that is used as a trocar for minimal invasive surgery (see Fig. 29). It contains a crescent shaped cutting blade at the distal end of the instrument. A trigger at the proximal end of the instrument extends the blade approximately 1 mm and immediately retracts it afterwards. By multiple blade extensions and retractions the tissue layers are carefully dissected until the abdominal area is reached.

Fig. 29: AutoSuture Visiport (Covidien), single sided axial cutting device [27].

An example from another field that uses single sided axial cutting is a vegetable chopper. In Fig. 30 an example of such a device is illustrated. Vegetable choppers use a cutter which is translated by delivering a normal force to a trigger. A spring is used to retract the cutting blade.

Fig. 30: Slap Chop vegetable chopper, single sided axial cutting [28]

A.2. Single-sided Radial Cutting

A.2.1. Coring Principle

- Steiner electromechanical morcellator [21]: the Steiner electromechanical morcellator (Karl Storz) consists of two concentric tubes. The outer tube is stationary and serves as a guide for the inner rotating tube. The inner tube has a sharpened distal end and is rotated at speeds between 200 to 300 rpm. A grasper is inserted in the inner tube to pull tissue towards the inner rotating tube. The inner tube subsequently cores out a cylindrical piece of tissue as long as the grasper exerts a pulling force on the grasped tissue. In Fig. 31 this instrument is illustrated.

Fig. 31: Steiner electromechanical morcellator (Karl Storz) [29].

- Wisap morcellator [30]: the Wisap morcellator contains a serrated/waved blade edge to core out tissue. The morcellators are available in a single cut or twin cut configuration. In the single cut configuration the morcellator contains one serrated cutting tube. In the twin cut configuration the outer edge and inner edge are serrated, providing two cutting edges. Both tubes rotated in opposite direction from each other, as is shown in Fig. 32.

There are two main models; the Power drive and Morc Drive mini. However, no additional information was found.

Fig. 32: WISAP Morcellator (twin cut). The direction of the rotating tubes is indicated with the brown arrows [31].

- Gynecare X-TRACT/ Diva FemRX [32]: the Gynecare X-TRACT (Ethicon) uses the same principle as the Steiner electromechanical morcellator. The tissue is cored out using a grasper which directs the tissue towards the circular rotating cutting tool. However, the main difference between the two instruments is that the X-TRACT has an extra inner stationary tube that prevents the tissue from twisting during removal (see Fig. 33).

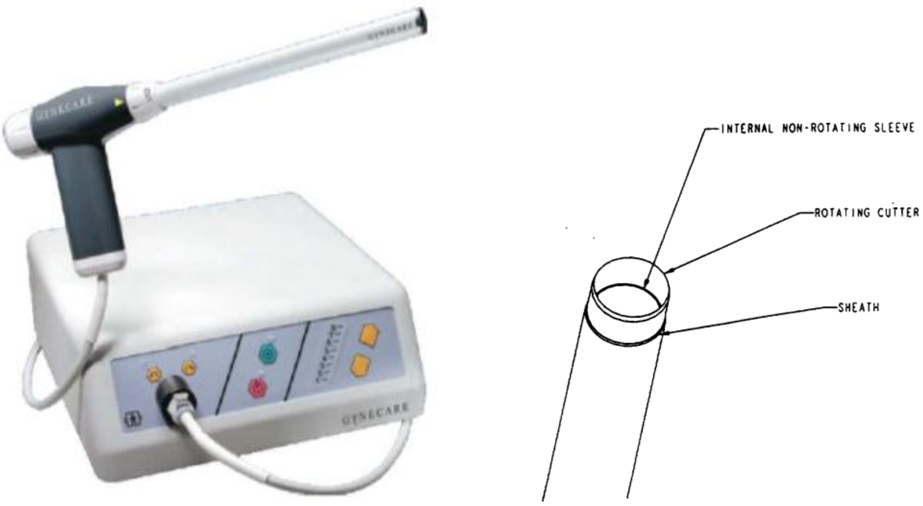

Fig. 33: Gynecare X-TRACT Morcellator [21, 32].

- HSEL morcellator [33]: the HSEL (high-speed electrical laparoscopic) morcellator (Cook) consists of two tubes; an inner rotary tube which has a cutting edge at its distal end for cutting tissue, and an outer stationary tube (see Fig. 34). Tissue is drawn towards the cutting edge of the inner hollow tube using constant aspiration/suction.

  Tissue is drawn in through the distal opening of the outer sheath. A sideways or circular motion needs to be made to the distal end of the instrument to bring the rotary inner edge in contact with the tissue and subsequently cut the tissue.

A.2.2. Peeling Principle

- Gynecare Morcellex [21, 34, 35]: the Gynecare Morcellex (Ethicon) uses a rotating circular blade and a stationary outer tube to morcellate tissue. The outer tube can slide over the inner cutting blade to provide safety to the surrounding tissue and to prevent the instrument to core out tissue. Instead of coring out a cylindrical tissue mass, this instrument is capable of peeling of pieces of tissue due to the oblique part of the outer tube. This has as advantage that a continuous removal process of the entire tissue mass is now a possibility.

  In Fig. 35 this instrument is illustrated. In the picture in the left corner the entire system is shown. The middle picture illustrates the tip of the instrument with the oblique outer tube in position for tissue peeling. The right picture illustrates the outer tube slid over the inner cutting blade to prevent tissue damage.

- Variocarve / Morce Power Plus [18, 21, 36]: the Variocarve (Olympus Medical Systems corp.) is the predecessor of the Morce Power Plus (Richard Wolf). Both morcellators use a similar working principle as the Morcellex. The main difference is that this instrument uses a custom trocar for insertion of the morcellators, whereas the Morcellex is inserted directly into the incision. In Fig.36 the Morce Power Plus is illustrated.

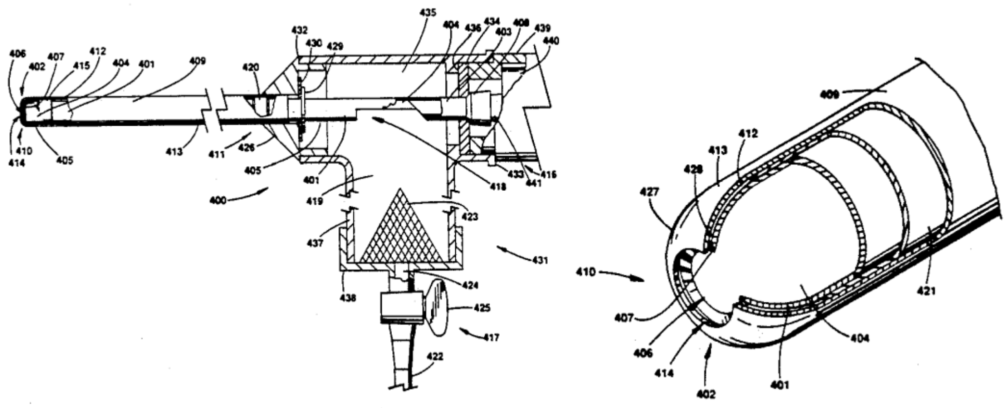

Fig. 34: HSEL Morcellator (Cook). Left: handpiece HSEL morcellator, Right: tip of the HSEL morcellator. Most relevant indicated numbers: 402: distal end of the morcellator, 406: distal opening of the inner rotary cutting member tube, 407: rotary open ended cutting edge, 414: distal opening of the outer tube [33].

Fig. 35: Gynecare Morcellex (Ethicon). Left: the Gynecare Morcellex, Middle: instrument tip with oblique outer tube in peeling configuration, Right: outer tube slid over cutting blade to increase instrument safety (prevention tissue damage) [24, 34].

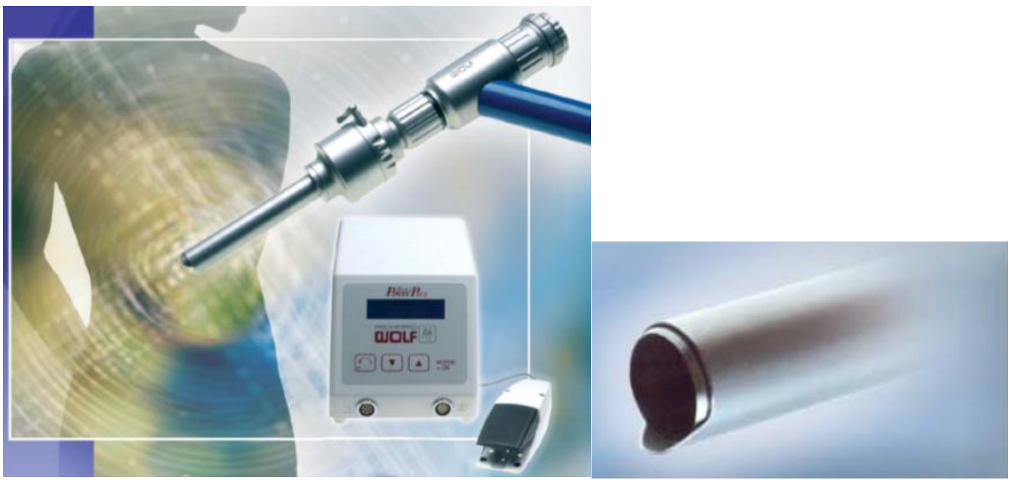

Fig. 36: Morce Power Plus (Richard Wolf). Left: the Morce Power Plus handpiece, Right: the distal end of the handpiece with the oblique sleeve and circular cutting blade [36].

- Rotocut G1: the working principle of the Rotocut G1 (Karl Storz) is identical to that of the Gynecare Morcellex. However, the Rotocut does have one added advantage over this system; the variable adjustable insertion/penetration depth [21, 37]. Space plates can be added around the shaft of the instrument to decrease the penetration depth of the instrument. In Fig. 37 this instrument is illustrated.

Fig. 37: Rotocut G1 (Karl Storz) morcellator using the peeling principle [37].

A.3. Double-sided Axial Cutting

A.3.1. Nibbling Principle

- Coherent EPM [38]: The Coherent EPM (Electrical Prostate Morcellator) consists of two tubes: a stationary outer tube and a translating inner tube. Positioned along the side of the stationary outer tube at the distal end of the morcellator are three ports were the tissue is drawn in using constant aspiration. Additionally, one port in the inner tube draws in the tissue to the center of the morcellator. The reciprocating movement of the inner tube then creates the cutting force relative to the outer tube.

  In Fig. 38 this instrument is illustrated in its initial and final position. The inner reciprocating cutting tube is indicated with the number 54. The tissue is drawn in using constant aspiration in the inner tube (64) and the ports in both the inner and outer tube (70 and 72). By the translating the inner tube the tissue is dissected and subsequently aspirated towards the end of the machine.

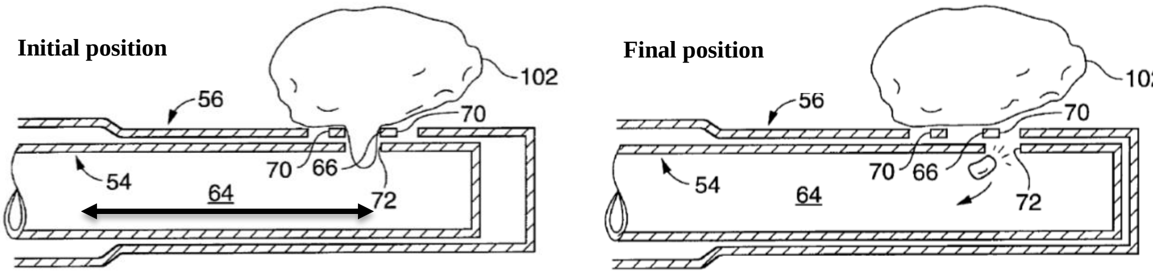

Fig. 38: Coherent EPM shown in patent US 006.156.049 A. The cutting tool of the instrument entails a reciprocating inner tube. The direction of the inner cutting tool is indicated with the arrow. 54: inner tube, 56: outer tube, 64: aspiration channel, 66: aperture outer tube, 70: ports, 72: aperture inner tube, 102: target tissue [38].

- Lumenis VersaCut [39]: the Lumenis VersaCut consists of an outer tube and inner reciprocating (translating) blade. Aspiration is used to draw in tissue into the opening of the outer tube and subsequently morcellate this tissue using a reciprocating inner cutting blade. In Fig. 39 this instrument is illustrated.

Fig. 39: Lumenis VersaCut morcellator. Indicated with the arrows are the inner reciprocating blades (which are not illustrated in the figure) [39].

- Smith and Nephew Truclear Ultra [40, 41]: the Truclear Ultra morcellator (Smith & Nephew) is very similar to the Lumenis VersaCut. A reciprocating blade dissects tissue that is drawn in by constant aspiration. In Fig. 40 this instrument is illustrated.

Fig. 40: Truclear Ultra morcellator (Smith and Nephew). The arrow indicates the direction of the inner reciprocating blade [40, 41].

A.4. Double-sided Radial Cutting

A.4.1. Shaving Principle

In Fig. 41 different shaver blades are illustrated. The different producers of the shaver blades are indicated in the columns and the amount and way the shaver blade the tissue removes is indicated in the rows. It can be seen that the most aggressive shaver blades utilizes serrated blades to tear and rip the tissue, whereas the standard shaver blades use a sharpened tip to cut the tissue. In a study of Wieser et al. (2012) it was determined that the most aggressive shaver blades with the serrated blades resected more tissue (in mg/min) than standard shaver blades [23]. Next to this it was determined that all shaver blades have an optimal rotational speed and pressure at which the shaver blade is pushed against the tissue. The type of shaver blade that is most effective, dependents highly on the tissue type, with the most optimal shaver blade for tendon resection being the “aggressive +” blades.

Examples shaver blade models:

- Dionics Power shave blade [42]: the Power shave blade (Dionics) consists of two tubes; an inner rotating tube and outer stationary tubes. Both tubes contain an opening with serrated edges (shaver blades) positioned at perpendicular to the distal end of the instrument. Tissue is shaved off, due to the relative motion between the inner and outer tube in combination with the opposing teeth between the inner rotating tube and outer stationary tube. Aspiration is used to draw in the tissue. In Fig. 42 this instrument is illustrated.

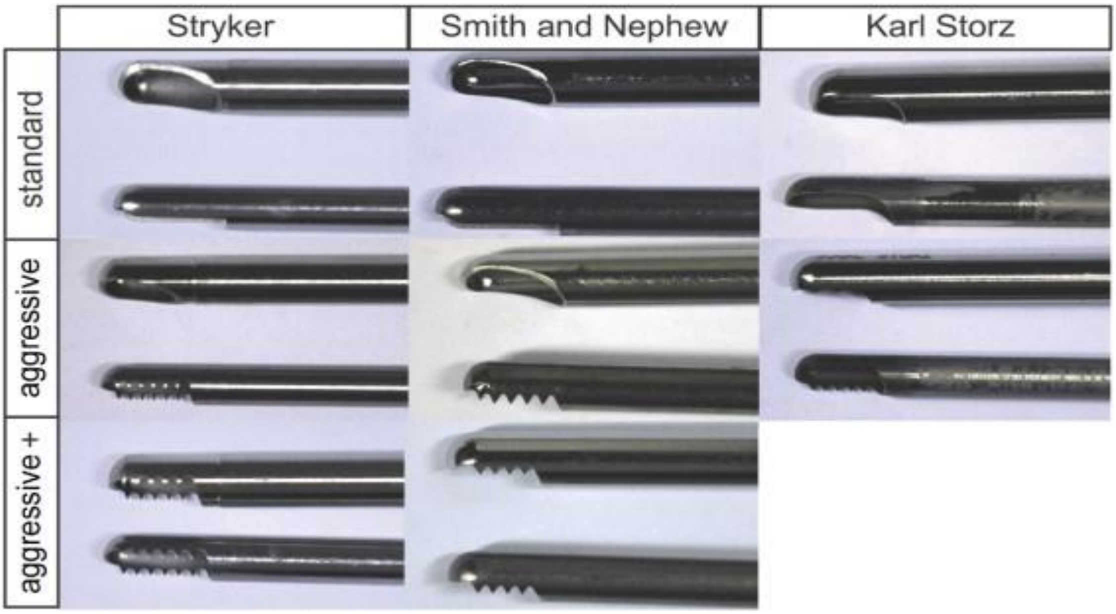

Fig. 41: Different shaver blades [23].

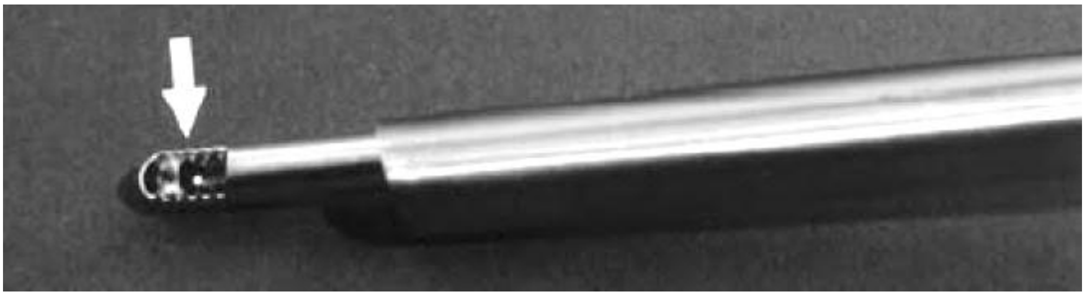

Fig. 42: the Power shave blade (Dionics). The rotating cutting edge is indicated with the white arrow [42].

- Smith & Nephew Truclear Rotary [43]: the Truclear Rotary morcellator (Smith & Nephew) utilizes the same working principle as the Power shave blade. In Fig. 43 this instrument is illustrated.

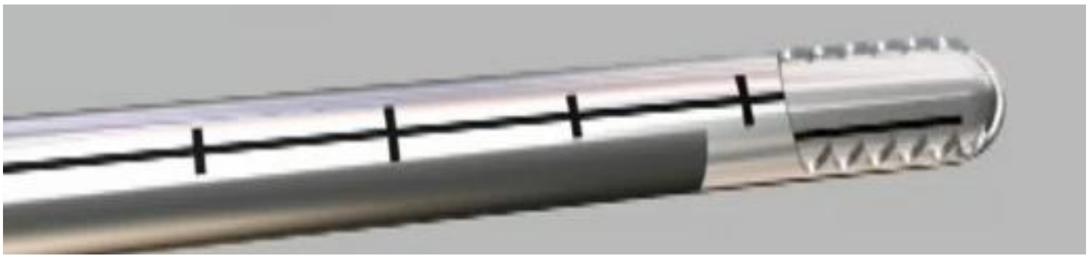

Fig. 43: the Truclear Rotary morcellator (Smith and Nephew)[43].

- Karl Storz Powershaver SL pro line [44]: the Powershaver SL Pro line (Karl Storz) features inner cutting blades with three cutting edges. The shaver blades are illustrated in Fig. 44.

Fig. 44: Pro Line shaver blades of Karl Storz [44].

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APPENDIX C: BRAINSTORM SESSIONS

To find potential solutions for the design of the morcellator for the surgical treatment of Cushing's disease in horses, multiple brainstorm sessions were held. In Fig. 45 and 46 these brainstorm sessions are schematically illustrated. In Fig. 46 it also becomes clear that axial translation is not possible with double-sided frontal resection.

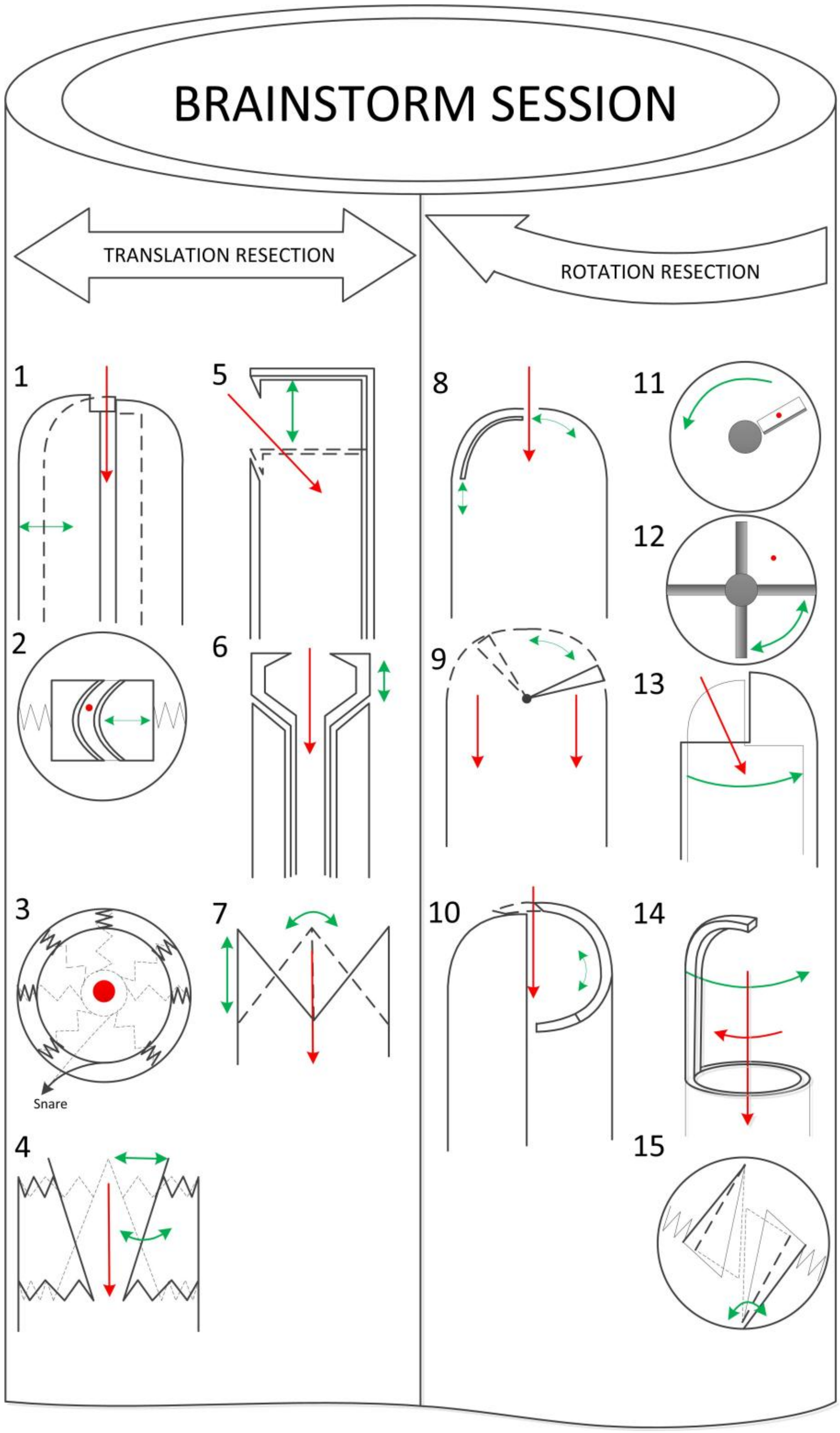
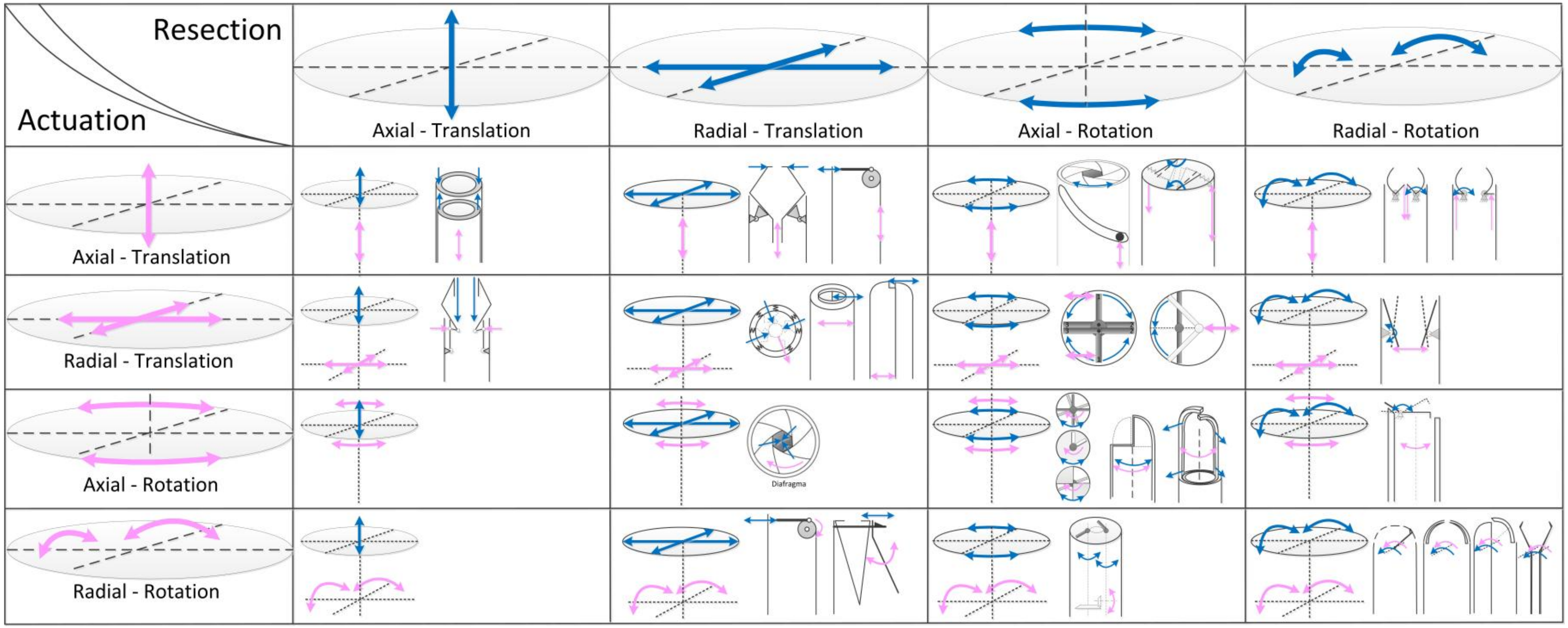


Fig. 45: Brainstorm session 1, design solutions are subdivided into the direction of motion of the resection tool; translation or rotation. The red arrow indicates the direction of the tissue and the green arrows indicate the direction of motion of the resection tool.

Fig. 46: Brainstorm session 2. The brainstorm ideas are subdivided into the direction of motion of the resection tool (axial translation, radial translation, axial rotation and radial rotation) and the direction of motion of the drive element (axial translation, radial translation, axial rotation and radial rotation). The blue arrows indicate the direction of motion of the drive element and the blue arrows indicate the direction of motion of the resection tool.



APPENDIX D: PROOF OF PRINCIPLE REPORT

In this Appendix the test protocol followed during testing will be discussed, as well as a short report of the actual test day.

D.1. Test Protocol

D.1.1. Method

Test set-up

The test set-up as illustrated in Fig. 47 will be used for the proof of principle experiment.

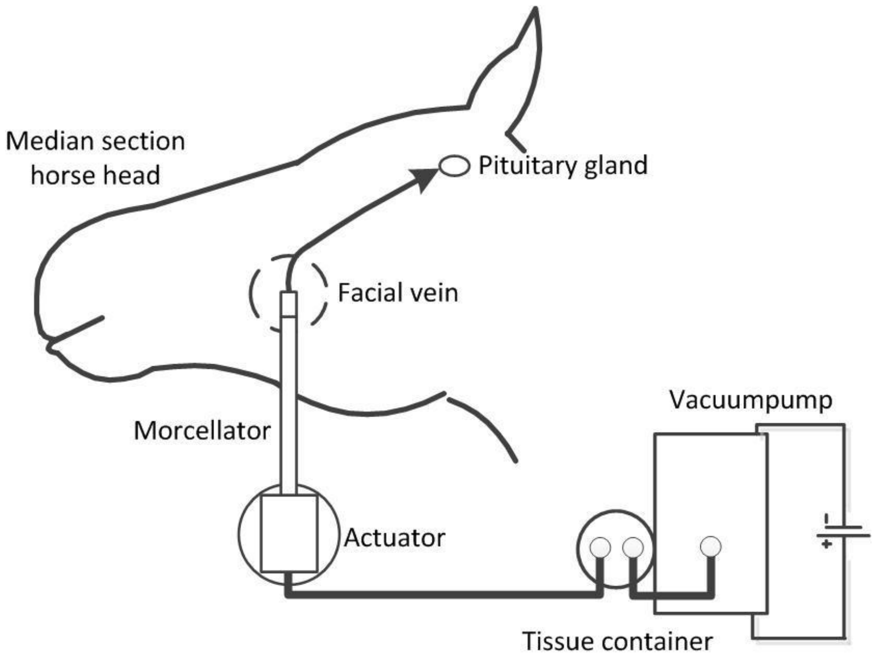


Fig. 47: Test set-up during proof of principle experiment.

Preconditions

Before the tests could commence the following preconditions needed to be met:

- Morcellator prototype
  - *Fully assembled, cleaned and functional*
- Actuator
  - *Fully functional and cleaned*
- Vacuum pump
  - *Fully functional*
  - *Connected to the power outlet*
- Tissue container
  - *Clean and airtight for achieving sufficient aspiration*

Testers

Supervision: Expert veterinarian
Tester: Aimee Sakes

Test execution

The following steps will be taken to execute the test:

- Horse head preparation:

Horse head cadaver is drained of blood
The skull is divided into two median sections using a bone saw
The brain is removed from both median sections
Horse head cadaver is positioned on a table (adjustable in height)
Incision is made to expose the facial vein
After exposure of the facial vein, an incision is made in the facial vein to gain entry

- <u>Morcellator preparation:</u>
  The tissue container and vacuum pump are positioned on the table
  The two tubes from the tissue container are connected to the vacuum pump and morcellator
  The morcellator is tensioned by using an adjustable mass that hangs freely at the side of the table
  The mass is increased until the needed tension is created.
  → *Required cable tensioning determined*
  The morcellator is inserted in the facial vein
  The morcellator is guided through the incision towards the pituitary gland
  Visual confirmation of the right positioning of the morcellator at the pituitary gland
  Start morcellation process by turning on the vacuum pump and actuator
- <u>Measurements:</u>
  Record the entire proof of principle experiment with a photo camera
  Record the morcellation process with a camera
  → *Rotational speed*

<u>Test planning</u>
The tests are executed in the Faculty of Veterinary medicine in Utrecht at 13 September 2013.

D.1.2. Materials

<u>Biological tissue</u>
- For the testing purpose one horse head is drained of blood.
- The head should be no older than a day to prevent clogging of the veins.
- No known abnormalities to the vascular system should be present.
- The horse should not suffer from an infectious disease prior to euthanasia.

<u>Test parts</u>
The entire flexible morcellator will be tested including:
- The flexible shaft of the morcellator
  - Drive element design
- The actuation mechanism of the morcellator
  - Actuator
  - Tensioning mechanism
- The aspiration mechanism of the morcellator
    - Vacuum pump
    - Tissue container
    - Tissue transportation channel
- The resection tool design of the morcellator

The working principle of above mentioned parts will be validated during the tests. Furthermore, the above mentioned parts will also be tested based on the following measurable quantities:
- Rotational speed resection tool
- Required cable tensioning for smooth resection

<u>Required additional tools</u>
The following additional tools are needed to perform the test:
- Bone saw

Saw for the removal of the skull

- Adjustable table
  Table for horse head positioning
- Scalpel blade
  Incision in facial vein
- Multiple pincers
  Exposing the facial vein
- Calibrated masses
  For cable tensioning
- Screwdriver
  Fastening and opening of the handle piece
- Photo camera
  Record the process of the proof of principle experiment
- Video camera
  Recording rotational speed during morcellation

D.1.3. Results

Test results

The test results will be recorded on a photo camera, discussed in this thesis and finally conclusion and recommendations will be made.

D.2. Test Report

At Friday 13th of September the HORSE morcellator was tested at the Faculty of Veterinary medicine of the University Utrecht. The test was performed in the section hall were all post mortem biopsies take place. The section head of this department, Louis van der Boom, had arranged for a fresh cadaver Friesian horse head. Assistance was given by Filip Jelinek and Paul Henselmans of the TUDelft.

The determination of the required cable tensioning was executed by using multiple calibrated masses that could be connected to the cable end of the morcellator. Smooth motion transference from the cable drive element towards the resection tool was seen at a cable tensioning of 3 N.

The testing of the HORSE morcellator prototype began with the division of the horse head in two median sections. For this purpose a large electrical bone saw was used to first cut off the nose of the horse head and subsequently divide the horse head into two median sections. After obtaining two median sections, the brain was removed to get a good view of the pituitary gland. Using previous knowledge gained during the experiments for tip dimension determination, the facial vein was exposed by making an incision into the horse head close to the supposed position of the facial vein. The facial vein was dissected from the surrounding tissues and an incision was made into the vein to get an entry point for the morcellator. Furthermore, the vascular path of the facial vein was followed for a few centimeters for confirmation about the correct vessel and vascular path. After visual confirmation that the correct vein was exposed, the HORSE morcellator was inserted.

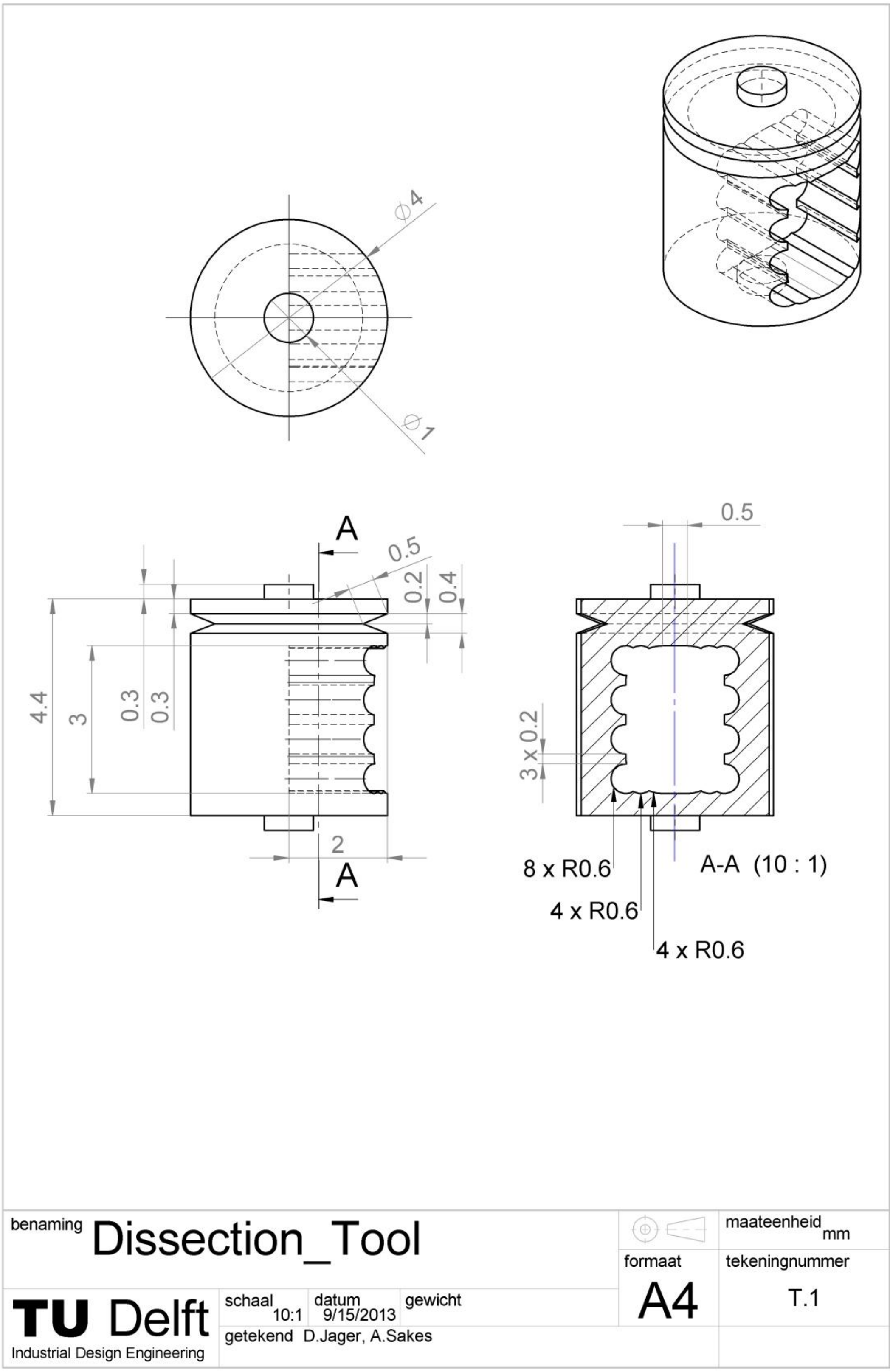
The HORSE morcellator was passively steered through the vascular system by pushing at the proximal end of the morcellator and following the curves of the vascular system. The insertion process was considered relatively easy to perform, as a non-clinician could perform it, and did not last longer than a minute. After full insertion, the horse head cadaver was turned around to confirm the correct positioning of the morcellator close to the pituitary gland. The inside of the median section of the horse head cadaver confirmed the correct positioning of the HORSE morcellator close to the pituitary gland, subsequently validating the endovascular approach for reaching the pituitary gland.

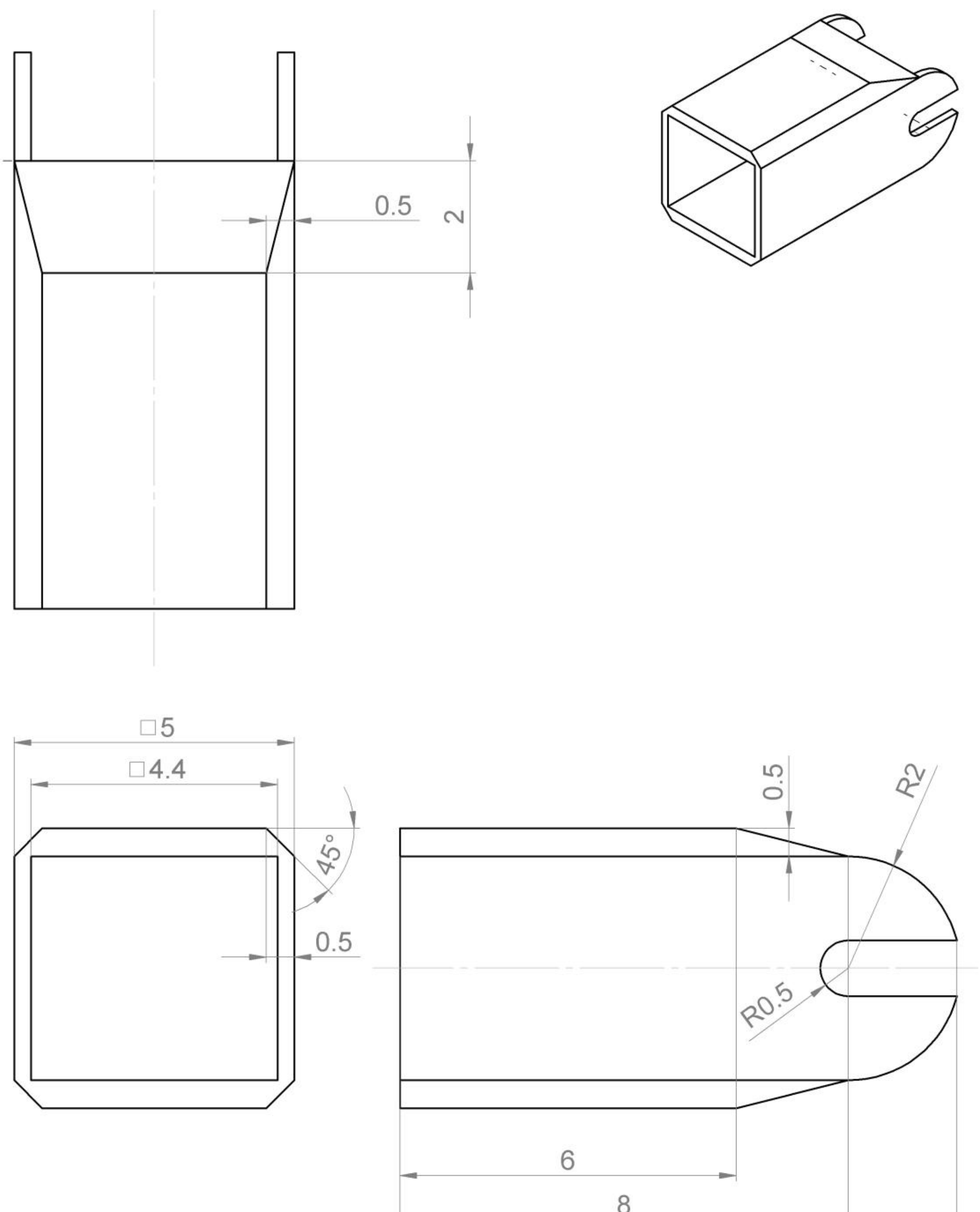
Once positioned at the pituitary gland, the morcellator was connected to the actuator and aspiration mechanism. First, the aspiration mechanism was turned on to gain direct tissue contact with the pituitary tissue. After full contact was achieved, the actuator was turned on and the morcellation process could commence. The HORSE morcellator was able to dissect the pituitary gland tissue using an average rotational speed of 75 rpm. The working principle of the morcellator was also tested on brain tissue to validate the morcellator. Both experiments were successful, validating the working principle of the aspiration mechanism, drive mechanism and resection tool design.

The HORSE morcellator did encounter some difficulties with the pulley and tensioning mechanism. The cable got tangled around the drive axis, inside the ball bearings, and other cable end. A pincer was used to get the cable situated around the pulley again. However, some damage was observed due to kinking of the cable. Furthermore, it was difficult to keep the cable properly tensioned due to the length of the cable. This may have contributed to the tangling of the cable.

Overall, the test was considered a success. The endovascular approach for the surgical treatment of Cushing’s disease in horses is proven to be feasible. Furthermore, the working principles of the cable drive mechanism, resection tool design and aspiration mechanism are validated.

APPENDIX E: TECHNICAL DRAWINGS





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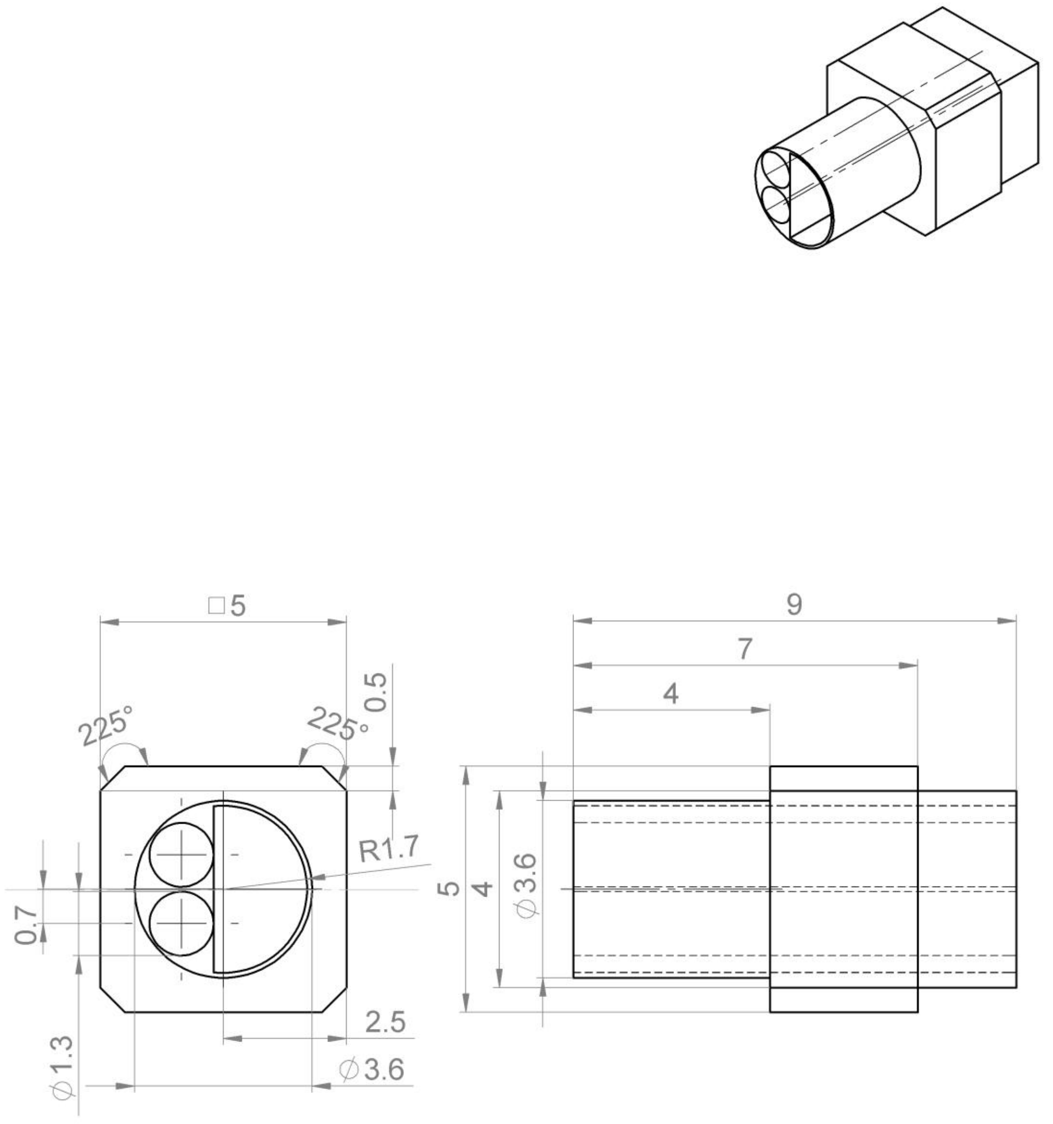
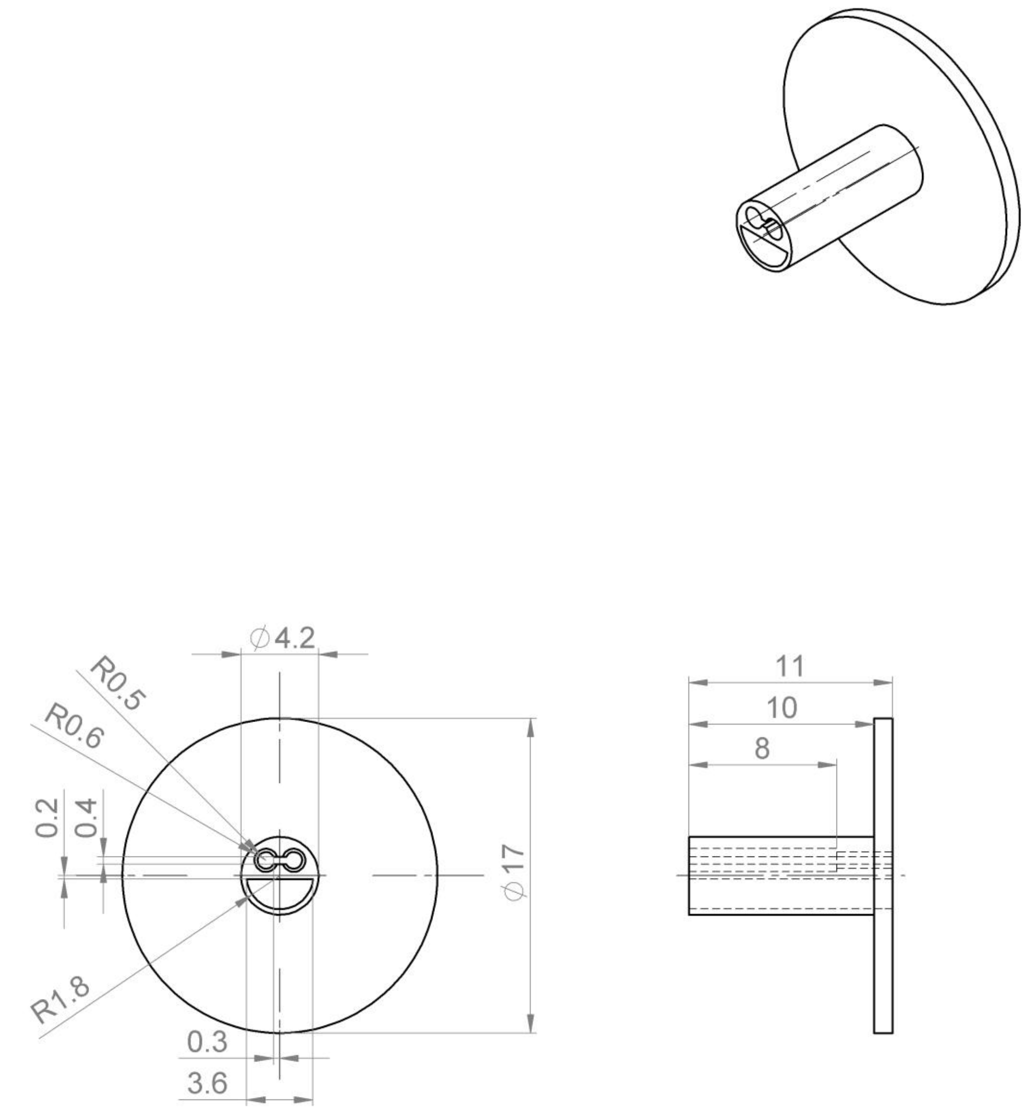
TU Delft	schaal 10:1	datum 9/15/2013	gewicht	A4	T.2
Industrial Design Engineering	getekend D. Jager, A.Sakes				



benaming **Connection_piece_1**

benaming Connection_piece_1			maateenheid mm
		formaat	tekeningnummer
TU Delft Industrial Design Engineering	schaal 8:1	datum 9/15/2013	gewicht	A4	T.3
	getekend D.Jager, A.Sakes		



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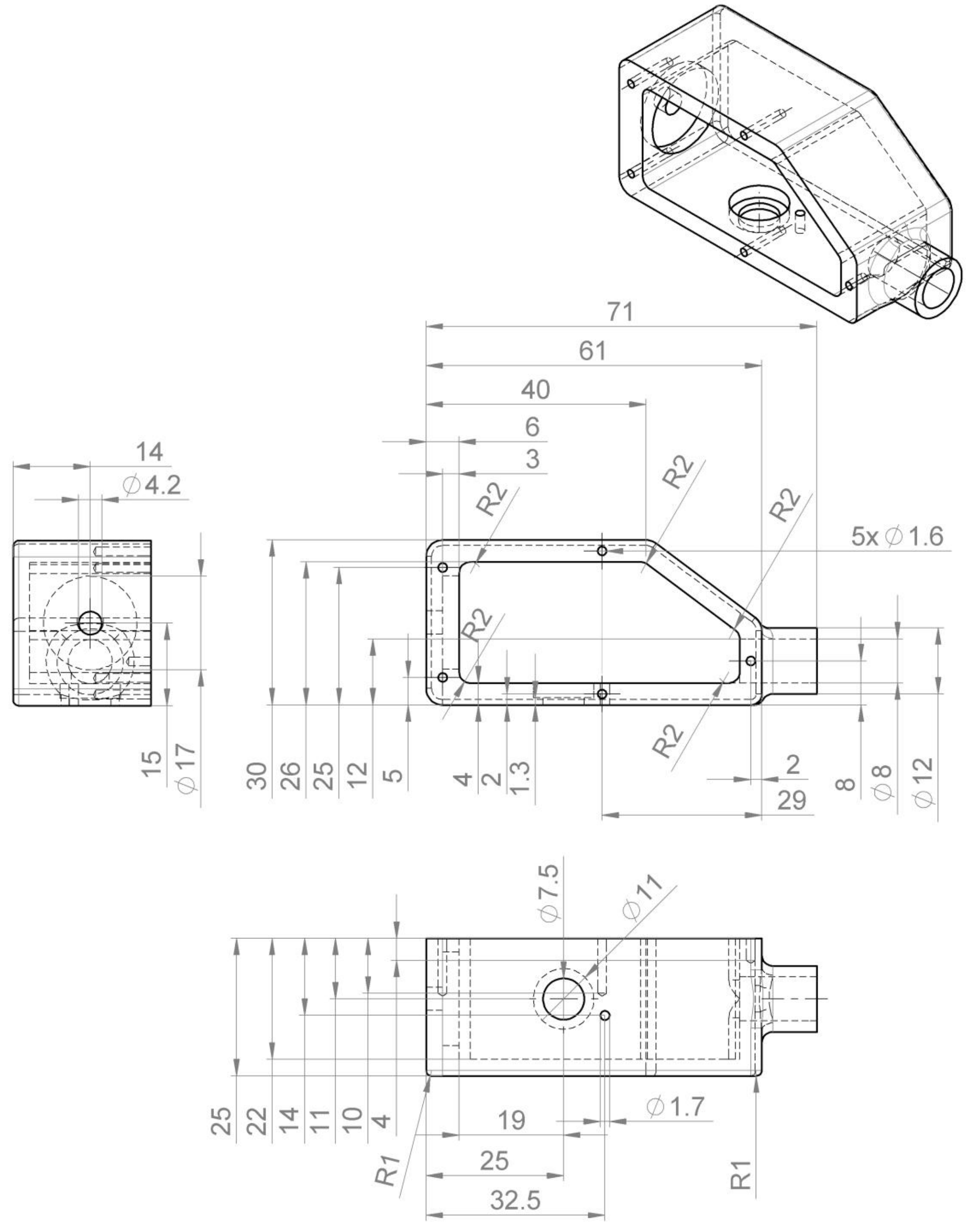
			formaat **A4**	tekeningnummer H.1
TU Delft Industrial Design Engineering	schaal 3:1	datum 9/15/2013		
	getekend D.Jager, A.Sakes			groep



Unspecified fillets R3

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				formaat	tekeningnummer
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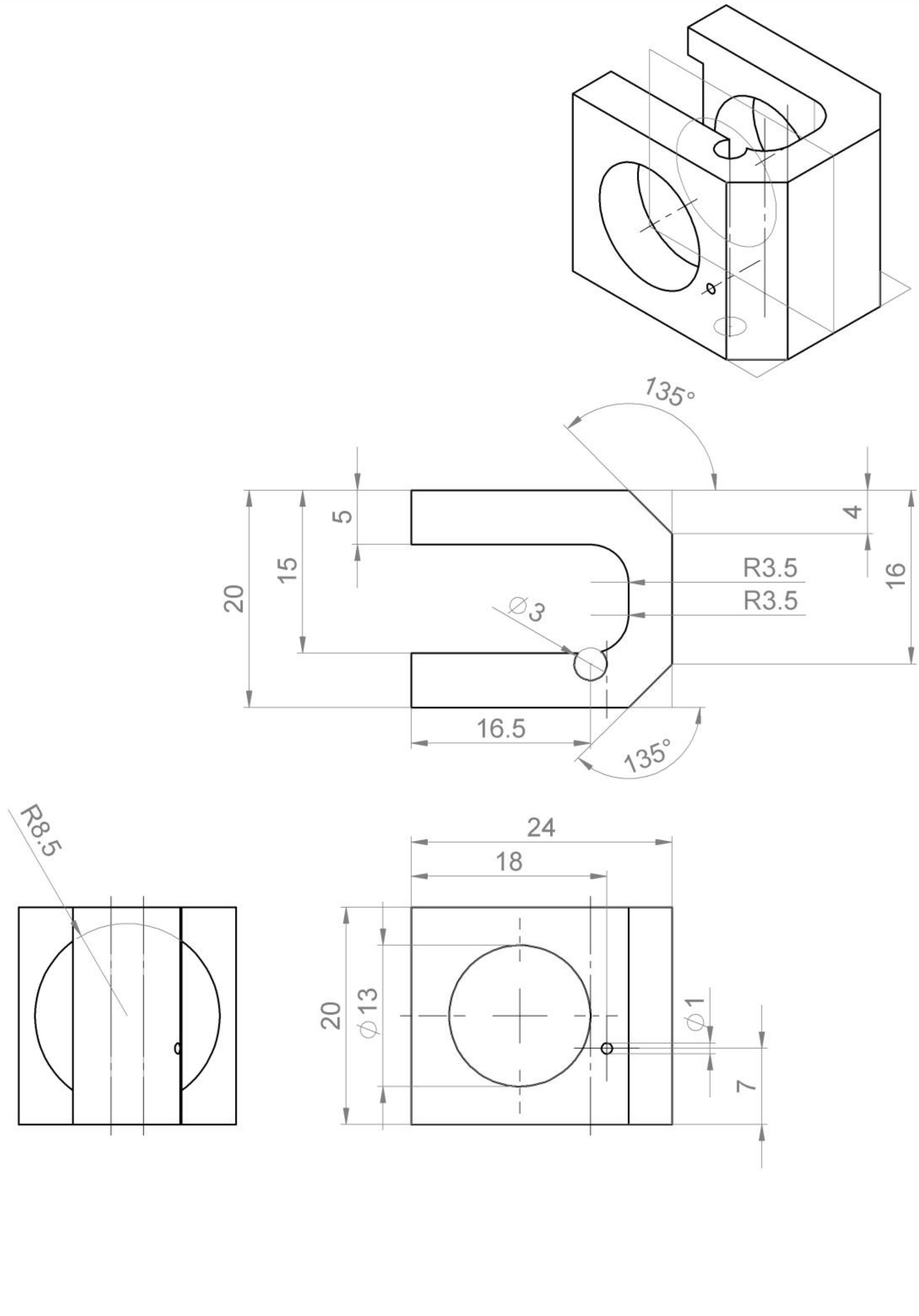
	getekend A. Sakes (4044827)				



benaming **Bearing housing**

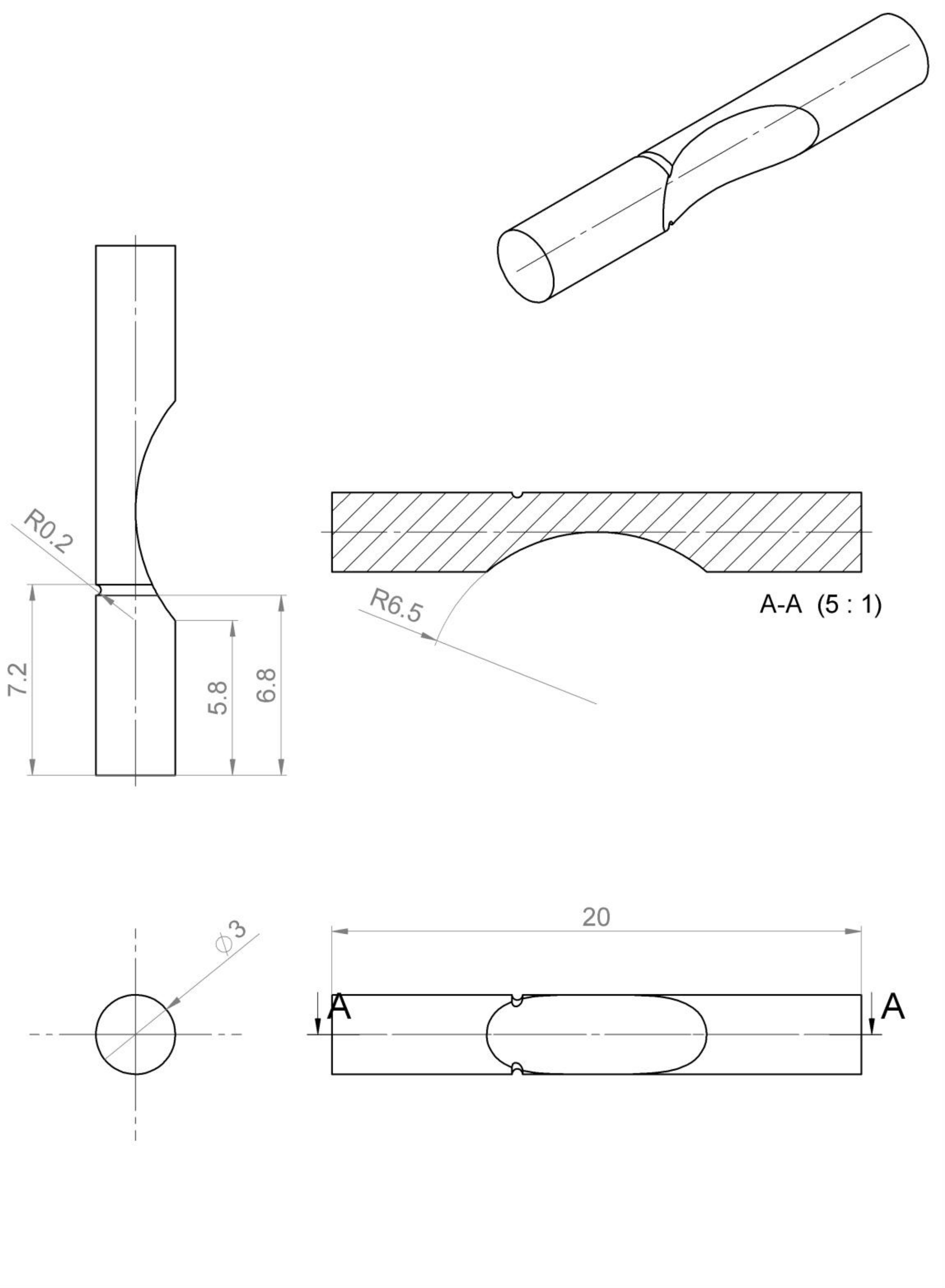
maateenheid mm

formaat A4

tekeningnummer H.3

TU Delft
Industrial Design Engineering

schaal 2:1
datum 9/15/2013
gewicht 10.32 gram
getekend D.Jager, A.Sakes



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				formaat	tekeningnummer
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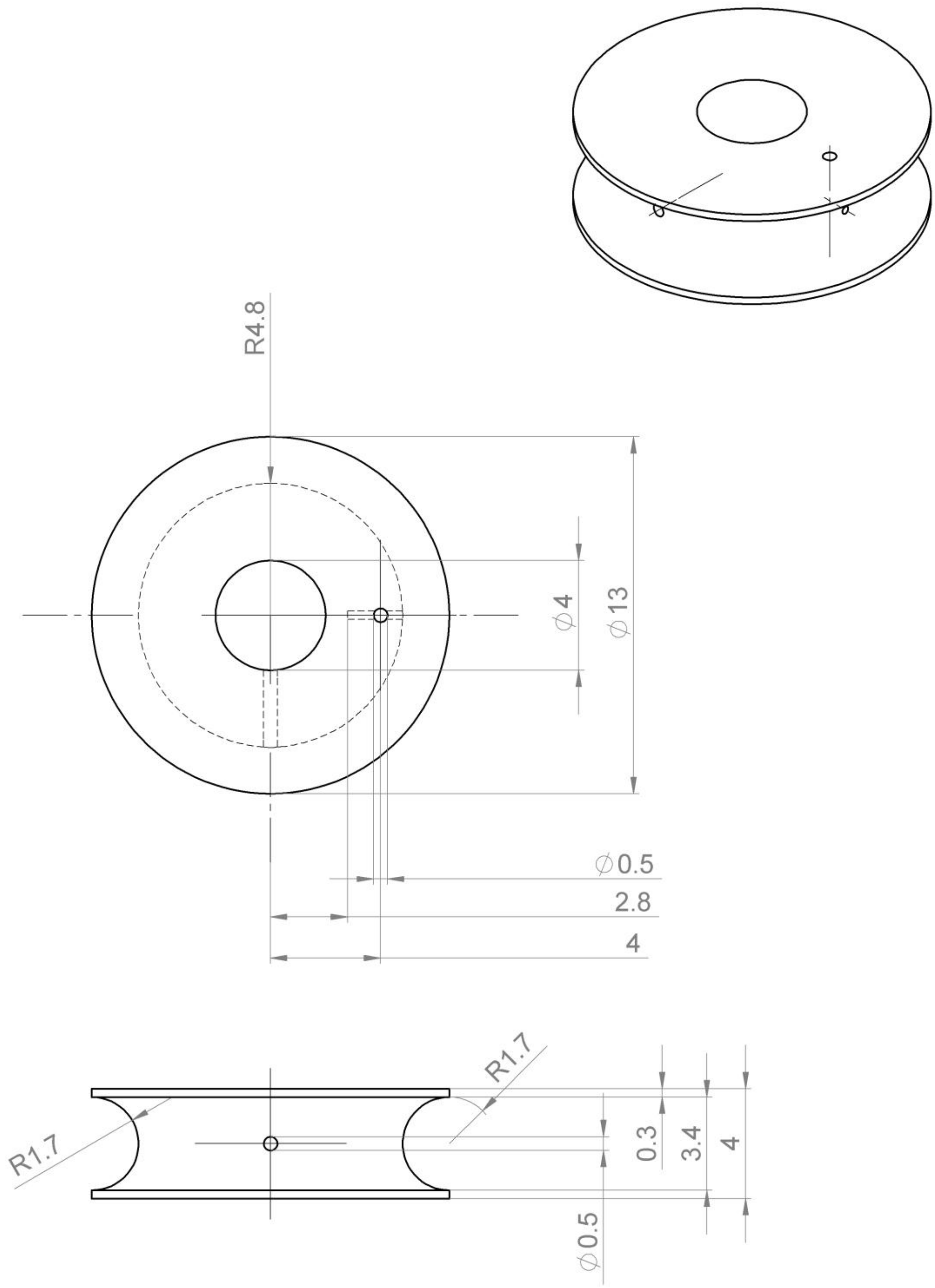
	getekend D.Jager, A.Sakes				



benaming **PULLEY**					maateenheid mm
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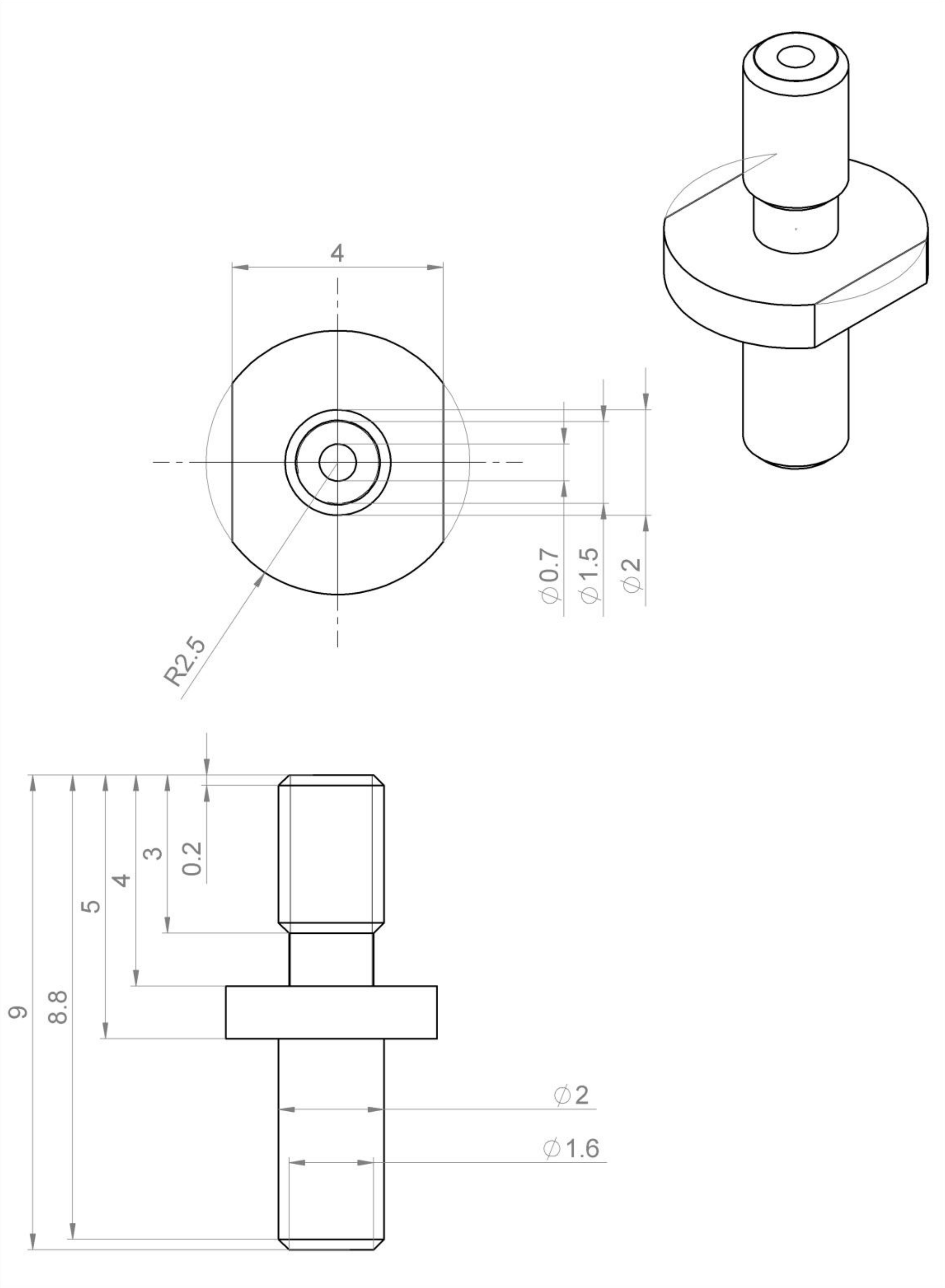

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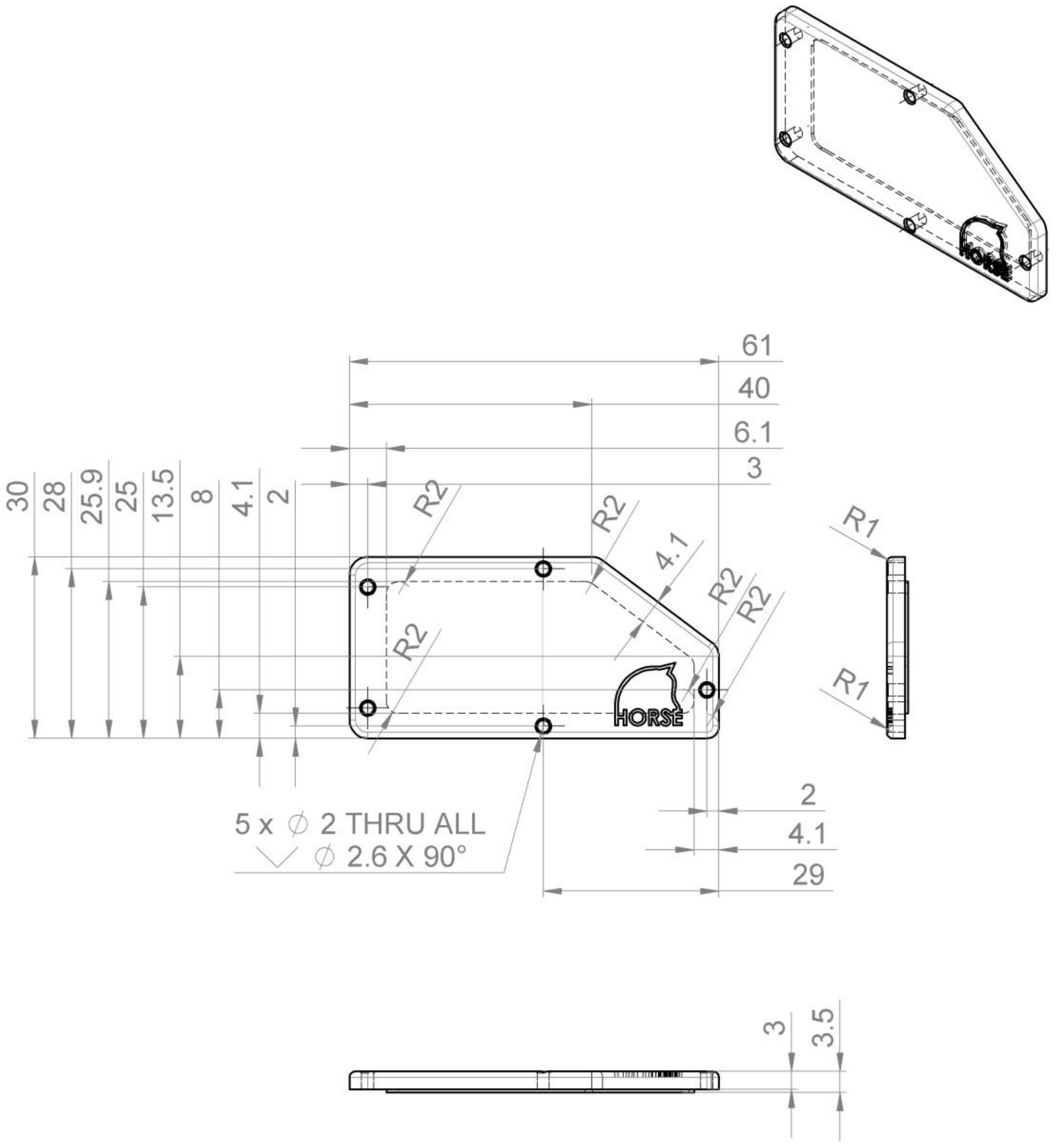

Unspecified fillets R3

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